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PAGET'S DISEASE: ITS PATHOLOGIC PHYSIOLOGY AND THE IMPORTANCE OF THIS IN THE COMPLICATIONS ARISING FROM FRACTURE AND IMMOBILIZATION*

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THE purpose of this paper is to call attention to the occurrence of acute atrophy of bone (osteoporosis) as a complication of Paget's disease, and to discuss the seriousness and implications of this situation as illustrated by two case histories. In order to make the subsequent presentation clear, it will be necessary first to discuss briefly normal bone metabolism, the metabolic abnormalities in osteoporosis as opposed to those in osteomalacia and osteitis fibrosa generalisata, the morbid anatomy of Paget's disease and finally a concept concerning the pathologic physiology in Paget's disease. It is regretted that some repetition of previous presentations[1-4] is unavoidable.

NORMAL BONE METABOLISM

Normal bone is composed of an organic matrix in which is deposited a calcium-phosphate-carbonate salt. It has three types of surface — one on which nothing is happening, one on which bone is being resorbed and one on which bone is being formed (Fig. 1). Where bone is being resorbed, one sees osteoclasts. Bone formation consists of two steps — the laying down of the matrix by osteoblasts and the deposition therein of the calcium salt.

It should be emphasized that bone formation and bone resorption occur at one and the same time. The reason why the body can deposit calcium on one surface while it is being resorbed on another is probably connected with the enzyme phosphatase. It is thought that the enzyme is made by the osteoblasts and that its presence where bone matrix is being formed increases the local concentration of phosphate ions by the splitting off of these ions from organic phosphate compounds, and hence promulgates the deposition of a calcium-phosphate-carbonate salt. In the absence of hepatic disease, the serum alkaline phosphatase level is an index of the activity of the osteoblasts. In the presence of excessive osteoblastic activity the serum phosphatase level rises; with osteoblastic inactivity it tends to fall. Since the normal level of the serum phosphatase is extremely low, however, this fall is not usually discernible.

There is considerable evidence that stresses and strains strongly stimulate the osteoblasts to lay down bone matrix; the greater the stresses and strains, the greater is the bone formation. Thus, persons whose occupations involve considerable physical activity have heavy skeletons, whereas those with sedentary occupations tend to have light bones.

OSTEOPOROSIS, OSTEOMALACIA AND OSTEITIS FIBROSA GENERALISATA

Osteoporosis, osteomalacia and osteitis fibrosa generalisata have one thing in common, a decreased bone mass. The total bone mass may be diminished to a pathologic degree from either an increase in bone resorption or a decrease in bone formation. The former is called "osteitis fibrosa generalisata" (Fig. 1) and is found in hyperparathyroidism. As will be seen later, it has certain points in common with Paget's disease. A decrease in bone formation may result either from an underactivity of the osteoblasts in laying down bone matrix or from a failure in the deposition of calcium salts in this matrix; the former is termed "osteoporosis," and the latter "osteomalacia" (Fig. 1).

Since the cases to be reported represent, in the final analysis, the imposition of osteoporosis on Paget's disease, it is desirable to discuss this condition in more detail. The causes of osteoporosis include old age, lack of stresses and strains to stimulate the osteoblasts, — for example, immobilization,[3] — lack of estrin to stimulate the osteoblasts — for example, postmenopausal osteoporosis[1, 2] — and lack of protein to provide material for the matrix, such as is found, according to our conception, in

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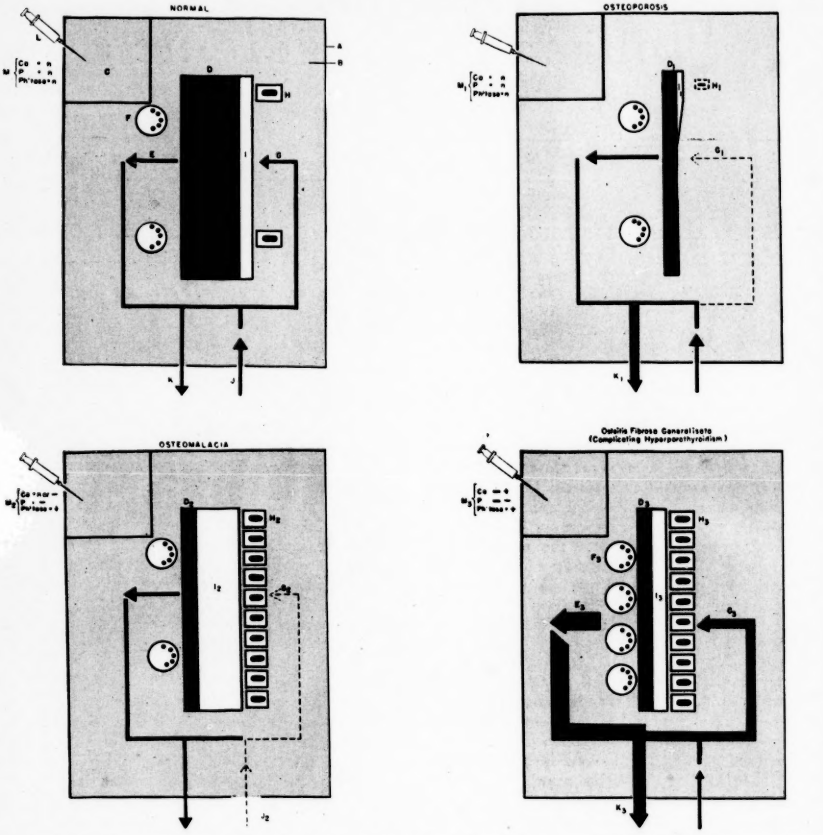

FIGURE 1. *Schematic Diagrams Showing the Differences in Bone Metabolism between Normal, Osteoporosis, Osteomalacia and Osteitis Fibrosa Generalisata Complicating Hyperparathyroidism (reproduced by permission of the* Journal of the American Medical Association).

In all the diagrams, the designations are as follows: A — *body limits;* B — *body fluid;* C — *body serum, a compartment of body fluid easy to tap for analysis;* D — *bone mass with two surfaces, one where bone is being resorbed and one where it is being laid down;* E — *arrow indicating by its size the rate of calcium and phosphorus resorption;* F — *osteoclast;* G — *rate of calcium and phosphorus deposition;* H — *osteoblast laying down osteoid* (I)*;* J — *calcium and phosphorus entering the gastrointestinal tract;* K — *calcium and phosphorus leaving the body by the kidneys and other exits;* L — *syringe for obtaining serum for analysis;* M — *blood values* (N, *normal;* +, *high; and* −, *low*).

NORMAL. Note that the deposition of calcium and phosphorus (G) *equals the resorption* (E) *and that part of the latter goes back into the bone.*

OSTEOPOROSIS. Note the decrease in bone mass (D_1), *the primary hyperplasia of osteoblasts* (H_1), *the decreased deposition of osteoid* (I_1); *the decreased deposition of calcium and phosphorus* (G_1), *the increased excretion of calcium and phosphorus* (K_1) *and the normal blood values* (M_1).

OSTEOMALACIA. Note the decrease in bone mass (D_2), *the hyperplasia of osteoblasts* (H_2) *because of increased stresses and strains, the increased deposition of osteoid* (I_2) *inadequately calcified because of the low serum calcium and phosphorus values, the decreased deposition of calcium and phosphorus* (G_2), *the primary difficulty in absorbing calcium and phosphorus from the gastrointestinal tract* (J_2) *and the abnormal blood values* (M_2).

OSTEITIS FIBROSA GENERALISATA COMPLICATING HYPERPARATHYROIDISM. Note the increased excretion of calcium and phosphorus in the urine (K_3), *the increased resorption of calcium and phosphorus* (E_3), *the increase of osteoclasts* (F_3), *the decreased bone mass* (D_3), *the increased bone formation by osteoblasts* (I_3) *because of increased stresses and strains, the increased deposition of calcium and phosphorus* (G_3) *because the serum is not undersaturated in respect to calcium phosphate, and the high phosphatase level* (M_3).

Cushing's syndrome,[4, 5] in the osteopathies of starvation and probably in the demineralization associated with hyperthyroidism.

Osteoporosis being by definition primarily a disorder of tissue metabolism and only secondarily one of calcium metabolism, no alteration in the serum calcium and phosphorus levels is to be expected, nor is one usually found. Since in osteoporosis bone formation decreases and bone resorption continues unabated, however, hypercalciuria occurs, and may lead to the same kidney complications as are found in hyperparathyroidism, in which the hypercalciuria results from the hypercalcemia.

The degree of hypercalciuria — the diet being constant — depends on the discrepancy between bone destruction and bone formation. If osteoporosis develops gradually, this discrepancy is at no time great and hypercalciuria is not marked. If, on the other hand, bone formation suddenly stops in a nonosteoporotic skeleton, there is marked hypercalciuria — for example, artificial menopause or immobilization of the skeleton in a cast. Furthermore, in young subjects, in whom the turnover of bone is more prominent than in older ones, a sudden curtailment of bone formation results in a marked imbalance.

There was recently reported from this laboratory[3] the case history of an active fourteen-year-old boy who fractured his leg and had a large part of his skeleton immobilized by a cast. So great was the resulting decrease in bone formation that not only hypercalciuria but also hypercalcemia occurred. The cause of the latter was an inability of the kidney to excrete the calcium as rapidly as it came from the skeleton. Since the hypercalcemia suggested hyperparathyroidism, the patient was subjected to two operations in an effort to find a parathyroid tumor before the true situation became apparent. The hypercalcemia soon disappeared when he was mobilized. The cases reported below illustrate another situation in which a serious state from acute atrophy of disuse (osteoporosis) occurred.

Morbid Anatomy of Paget's Disease

If one defines a "localized bone disease" as any disease that is not generalized, Paget's disease is localized. It may be limited to one bone or be widely spread throughout many bones, but it is not generalized. One can almost invariably find somewhere a sharp line of demarcation between normal bone on one side and Paget's disease on the other. The very fact that Paget's disease is not generalized is strong evidence against its being a metabolic or endocrinologic disorder. The reader may well ask, "What about the bone cysts in hyperparathyroidism?" But these are secondary complications; the underlying lesion, decalcification, is generalized. The reader may then ask, "What about postmenopausal osteoporosis, in which the bone lesions tend to be confined to the spine and pelvis?" Here the disease is following a well-defined pattern; certain parts of the skeleton are more prone to involvement than others and the distribution of the lesions is not spotty but according to plan; it is not as though the twelfth thoracic and third lumbar vertebras were involved whereas the remaining vertebras were normal.

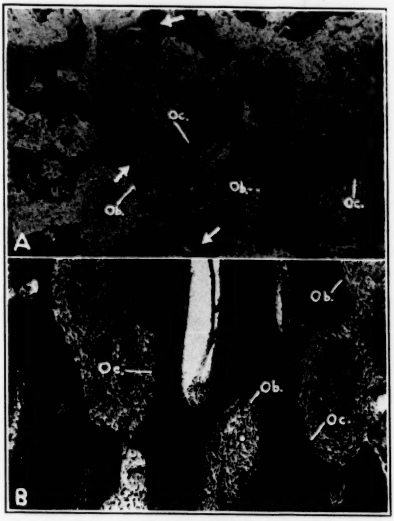

FIGURE 2. *Photomicrographs of the Bone in Paget's Disease* (A) *and Hyperparathyroidism* (B).

Note that although the osteoclasts (Oc.) *and the osteoblasts* (Ob.) *are present in both diseases the structural integrity has disappeared in* A *but is maintained in* B. *Note also the mosaic appearance of the cement lines, some of which are indicated by arrows.* (*These photographs were kindly supplied by Dr. Granville A. Bennett, to whom the authors are greatly indebted.*)

Having made the above rather dogmatic statement, we must make one reservation. We have in our clinic a patient with undoubted Paget's disease in whom every bone in the body is involved; moreover, each bone is at the same stage of the disease. Unfortunately, the patient refuses to be hospitalized for detailed studies.

When one comes to the actual bone lesion in Paget's disease, it has much in common with that seen in osteitis fibrosa generalisata (compare Fig. 2*A* and *B*). In both conditions the bone lesions are extremely vascular, there is marked fibrosis, about half the bone surface is covered with osteoclasts as evidence of marked bone resorption and about half with osteoblasts as evidence of marked bone repair, and the bone that is being laid down

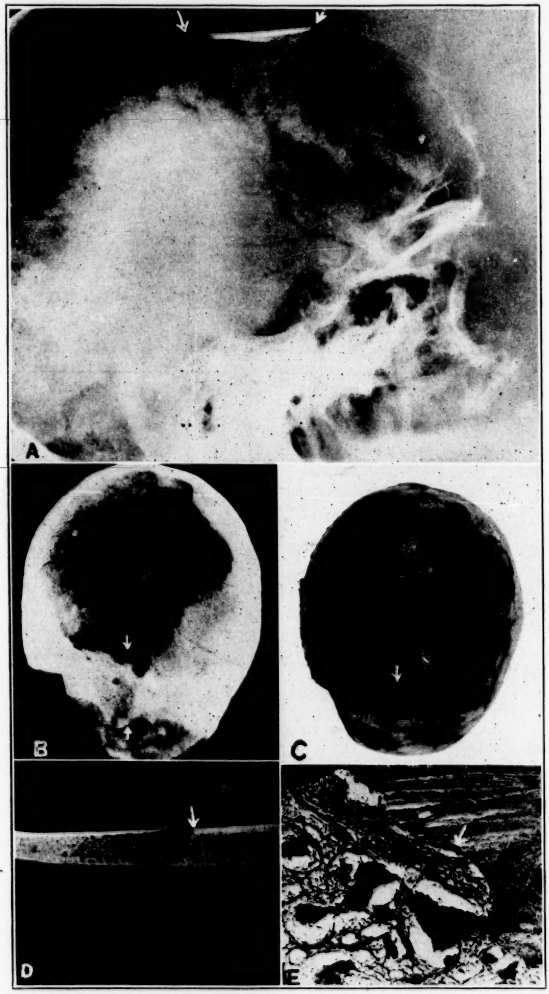

FIGURE 3. *Photographs Showing That the Initial Lesion in Paget's Disease is Bone Destruction.*

A — *the x-ray film of a skull with two areas of destruction separated by a bridge of normal bone (between the arrows).* B — *the x-ray film of the same skull post mortem.* C — *the skull as it appeared post mortem.* D — *a section through this skull showing the advancing edge of destruction (arrow), with normal bone to the right and involved bone to the left.* E — *a photomicrograph of the area at the point of the arrow in* D, *showing normal bone on the right and the initial lesion of bone destruction on the left with osteoclasts (arrow) in juxtaposition to the normal bone.*

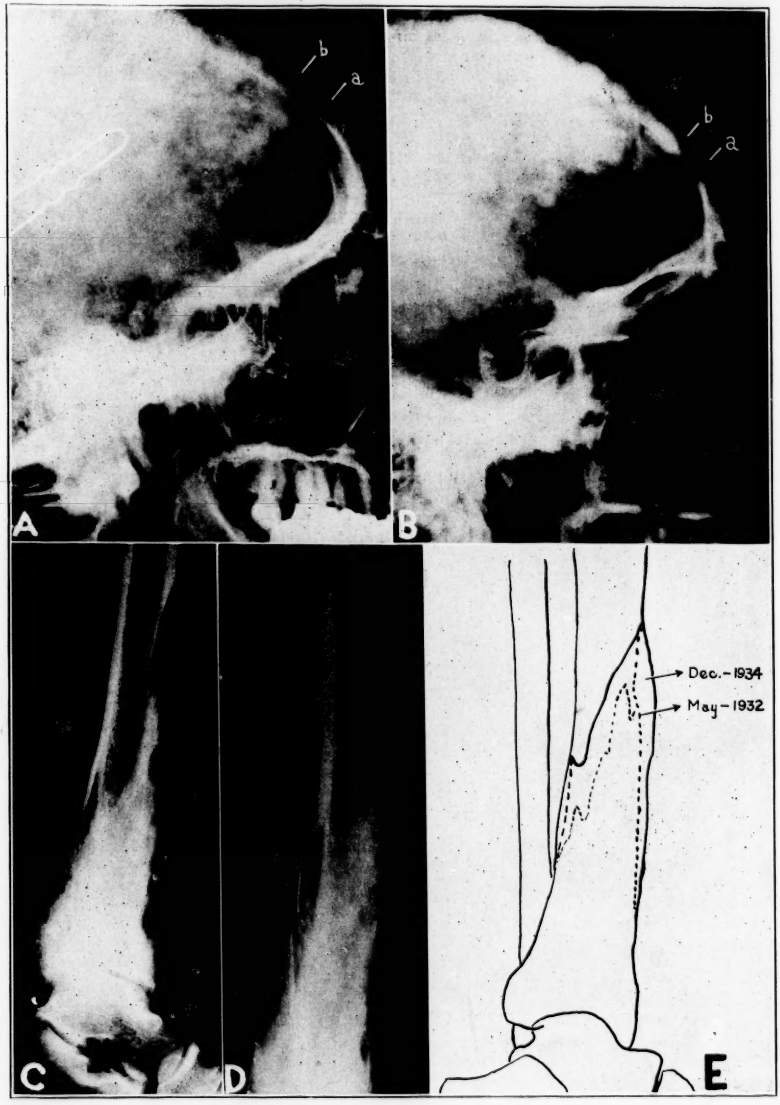

FIGURE 4. *The Progression of Paget's Disease.*

A — *skull showing an area of destruction*(a to b) *with normal bone to the right and overgrown bone to the left.* B — *the same skull two years later showing that the area of destruction has moved closer to the nose.* C — *involvement of the tibia.* D — *same tibia two and a half years later.* E — *diagram indicating the progression of the lesion in the tibia.*

is being calcified, as shown by the normal width of the osteoid seams. There are, however, some differences. There is not the same tendency to the formation of so-called "osteoclastomas" or brown tumors in Paget's disease as in osteitis fibrosa generalisata. The most important distinction between the two conditions, however, concerns the architecture of the bone. In Paget's disease, for reasons that will appear below, the trabeculae start nowhere and end nowhere; in osteitis fibrosa generalisata there may be extreme decalcification, but those trabeculae that are left are in good mechanical arrangement. A third difference between the two conditions has to do with the so-called "mosaic structure," as first described by Schmorl.[6] This pathognomonic feature of Paget's disease is due to the bizarre arrangement of the cement lines within the trabeculae (see arrows in Fig. 2). To be sure, there are other bone diseases with an increased number of cement lines in the trabeculae, but the lines are not so completely irregular. The reason for them will be discussed below.

From the above discussion, it is evident that in Paget's disease there is a marked increase in both bone destruction and bone formation; in other words, there is an increased turnover of bone. If one had to guess, one would presumably suppose that the increased bone formation was the result of increased bone destruction. But one does not have to guess; one can examine the initial lesion. To discover what is going on in a complicated pathologic picture, one should always try to get at the advancing edge of the lesion and see what comes first.

In the skull in Paget's disease one often finds lesions that have quite a different appearance from those encountered in other parts of the skeleton. They lack the marked overgrowth of bone and consist merely of circumscribed areas of bone destruction. The x-ray appearance of such a lesion is shown in Figure 3*A*. The involved area terminated abruptly (see arrows). At autopsy, a section through such an area (Fig. 3*D*) showed normal bone (to the right of the arrow) sharply demarcated from the involved bone (to the left of the arrow). A microscopic examination at this point (Fig. 3*E*) revealed normal bone (to the right) being destroyed by the destructive lesion (to the left), with numerous osteoclasts; no bone formation or osteoblasts were seen. This is strong evidence that the initial lesion in Paget's disease is bone destruction.

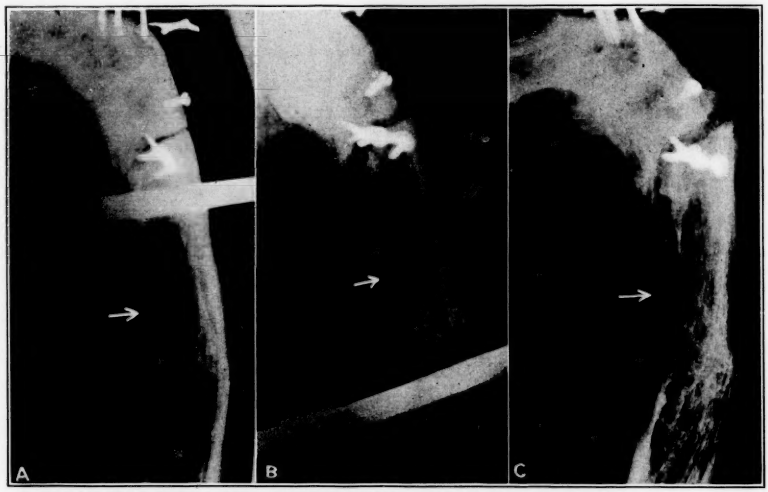

FIGURE 5. *X-ray Films of Paget's Disease (Case 1), Showing the Right Femur Immediately* (A), *Fourteen Weeks* (B) *and Seven Months* (C) *after the Fracture.*
Compare the densities of the cortex at the points indicated by the arrows.

Support for this contention can be derived from the characteristic manner in which the disease progresses. Thus, x-ray films of an involved skull (Fig. 4*A*) show three zones: normal bone (to the right of *a*), bone destruction (*a* to *b*) and bone repair with overgrowth and increased density (to the left of *b*). If such an area of involvement is followed for several years, the zone of bone destruction in some cases may be seen to advance. Such was the case in this skull, in which the lesion advanced into

the normal bone closer to the nose (Fig. 4*B*). In the long bones, for reasons that will appear below, the bone repair usually occurs almost simultaneously with the bone destruction, and one seldom has the opportunity to see one process divorced from the other; occasionally, where one does (Fig. 4*C*, *D* and *E*) the same sequence of zones appears. Schmorl[6] demonstrated that the initial lesion in the long bones is also bone resorption. He did this by making a longitudinal section of an involved long bone, from which he took a cross section 2 cm. distal to the point where the bone was involved grossly enough to be detectable by the naked eye. This cross section showed bone destruction without any evidence of bone formation.

TABLE 1. *Chemical Determinations in Case 1.*

DATE	BLOOD SERUM LEVELS				URINE		REMARKS
	CALCIUM	PHOSPHORUS	PHOSPHATASE	NONPROTEIN NITROGEN	CALCIUM QUASI-QUANTITATIVE TEST*	SPECIFIC GRAVITY	
	mg./100 cc.	*mg./100 cc.*	*Bodansky units*	*mg./100 cc.*			
8/14/41	—	—	—	—	—	1.028	Fracture; leg immobilized; milk ad lib.
8/30/41	—	—	—	—	—	1.008	Headache, anorexia, possible sinusitis and dysphagia
9/10/41	13.4	4.2	4.3	56	—	1.010	Epigastric distress, nausea and vomiting
9/26/41	13.2	4.1	—	68	+++	1.008†	Epigastric distress, nausea and vomiting
10/17/41	12.2	4.0	—	36	—	1.016	Patient somewhat better
10/30/41	—	—	—	—	—	—	Milk stopped; water forced.
11/ 5/41	10.3	3.6	6.1	—	+	—	Patient much better
11/13/41	—	—	—	—	—	1.017†	No complaints

*Sulkowitch test.
†Urine-concentration test.

CASE REPORTS

CASE 1* (M. G. H. 316138). The patient, a 58-year-old salesman, was admitted to the Phillips House on August 14, 1941. At the age of 22 he was aware of bowing of the left tibia. At the age of 28 he stepped into a hole and fractured the left tibia. X-ray examination revealed Paget's disease in the area of the fracture. This break healed without incident. At the age of 52 he fell down a flight of stairs and fractured the neck of the right femur. X-ray examination showed that this break also had been through an area of Paget's disease. The bones healed poorly, and finally a plate was inserted. Eight months after the fall, the patient was allowed to get about on crutches. He again fell and fractured the right femur in nearly the same place. He was placed in traction for 7 weeks and then in a plaster cast for 8 weeks. Eventually he was able to walk without crutches. On the day of admission, he was involved in an automobile accident, and for the third time fractured the neck of the right femur (Fig. 5*A*).

The past history revealed several interesting points. For many years the patient had consumed a large amount of milk — between 3 and 5 glasses a day. In his travels as a salesman, he had been in the habit of stopping for a milkshake several times a day, and in addition he had drunk milk at each meal. Also from time to time he had taken excessive amounts of alkalies for gastric distress. For more than 20 years he had been troubled with so-called "chronic sinusitis," with postnasal discharge and pain in the cheekbones.

Urinalysis shortly after admission showed a clear specimen with a pH of 5.0, a specific gravity of 1.028 and a slight trace of albumin. The sediment contained no casts, a rare red cell and 15 white cells per high-power field.

The leg was placed in traction, with a Kirschner wire through the lower end of the femur and a Hodgson splint with a Pierson attachment. The patient was allowed to take as much milk as he desired. He remained comfortable for 2 weeks, but then he began to complain of anorexia, headache and peculiar sensations of dryness in the back of the throat, associated with difficulty in swallowing. The patient attributed these symptoms to his "chronic sinusitis"; an otolaryngologist considered this probable, although he could find little on examination, and advised spraying the throat. The patient obtained no relief from this, but began to have epigastric distress, nausea and occasional vomiting. Urine examination at this time showed a specific gravity of 1.01, no albumin, a rare red cell and 2 white cells per high-power field. The serum nonprotein nitrogen was 56 mg. per 100 cc.

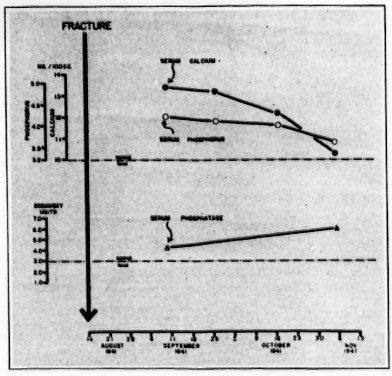

FIGURE 6. *Chart Illustrating the Effect of Fracture on the Serum Calcium, Phosphorus and Phosphatase Levels in Paget's Disease (Case 1).*

On September 10, 1941, approximately 4 weeks after the fracture, the serum calcium was 13.4 mg. per 100 cc., the serum phosphorus 4.2 mg., and the serum phosphatase 4.3 Bodansky units. These studies were repeated 2 weeks later with essentially similar findings (Fig. 6 and Table 1). At that

*This patient was seen through the courtesy of Dr. O. S. Staples and Dr. T. A. Warthin.

time the nonprotein nitrogen was 68 mg. per 100 cc. A urine concentration test showed that the specific gravity was fixed at 1.008, but a phenolsulfonephthalein test showed 20 per cent of the dye excreted in 15 minutes. During the next 3 weeks was permanently stopped and the intake of other fluids was increased. Within 1 week the patient was feeling much better. The serum calcium was 10.3 mg. per 100 cc., the phosphorus 3.6 mg., and the phosphatase 6.1 Bodansky units.

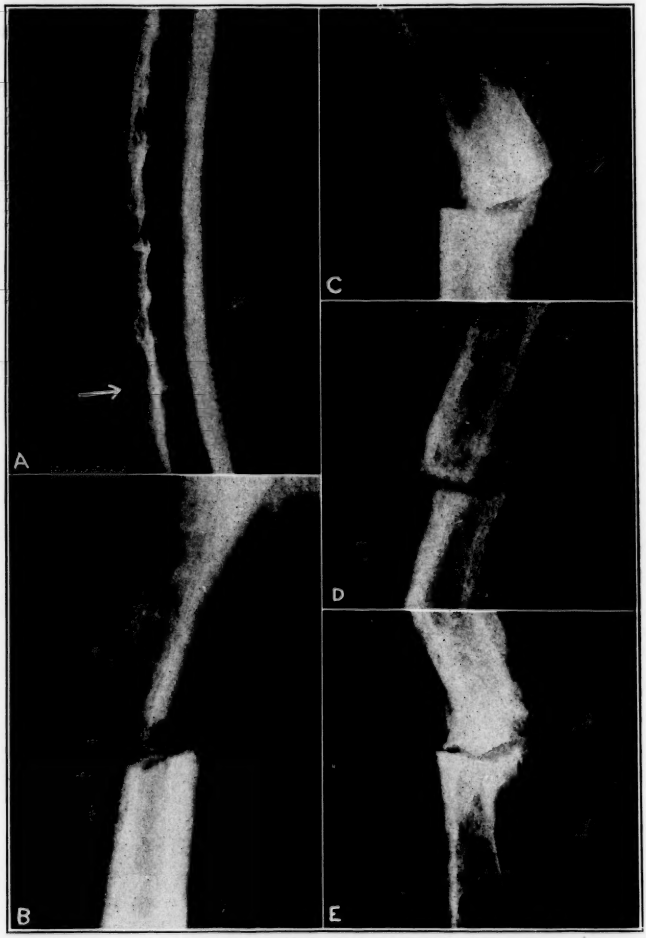

FIGURE 7. *X-ray Films of Paget's Disease (Case 2), Showing the Right Femur three years before* (A), *immediately* (B), *three weeks* (C), *five weeks* (D) *and ten weeks* (E) *after fracture. The point of fracture is indicated by the arrow. Compare the densities of the cortex in these films.*

the patient continued to have gastric distress. The water intake was increased and milk was omitted from the diet for several days; the serum findings were as follows: calcium, 12.2 mg. per 100 cc., phosphorus, 4.0 mg., protein, 6.4 gm.; and nonprotein nitrogen, 36 mg.

On October 30, because of our concept regarding the pathologic physiology of Paget's disease (see below), the milk He was able to concentrate his urine to a specific gravity of 1.017. Thereafter he had an uneventful convalescence, except that the fracture healed very slowly. He was discharged July 11, 1942, 11 months after admission.

CASE 2 (M. G. H. 281615). The patient, a 64-year-old woman, was admitted to the hospital on December 28, 1942,

with a fractured femur. At the age of 50 she became aware of enlargement of the head and the left clavicle. X-ray examination revealed Paget's disease. At the age of 57 she noticed bowing of the femurs. For some years she had been troubled with increasing deafness and ringing in the ears. She had never passed gravel. A physiologic menopause without hot flashes had occurred at the age of 52. In June, 1939, she was referred to one of us (F. A.) by Dr. Louis Hamman, of Baltimore.

The x-ray films of the femurs obtained in 1939 (Fig. 7*A*) had been used for teaching purposes to explain why it is possible in Paget's disease for a bowed leg to be as long as, if

FIGURE 8. *Paget's Disease Showing Fracture through the Site of a Previous Infraction.*
Other infractions above and below the fracture are indicated by arrows.

not longer than, the unbowed leg. (The question was raised and answered by Schmorl.[6]) It will be seen that a series of partial fractures occurred on the convex side that led to an increase in length of a fraction of a centimeter for each fracture. It can be appreciated that it would not be difficult to produce a complete fracture at one of these points. The site at which the fracture subsequently developed is indicated by the arrow. (That this is not an isolated occurrence is shown by an x-ray film of another case [Fig. 8], in which fracture occurred through one of the points of partial separation. Other points of infraction are indicated by the arrows.)

Physical examination in June, 1939, revealed the typical picture of Paget's disease, with great enlargement of the head, marked overgrowth of the jaws and enlargement of the left clavicle and both femurs. The blood pressure was 135/195. There were present a basal systolic murmur and a thrill that were interpreted as aortic stenosis on an arteriosclerotic basis. The serum calcium level was 10 mg. per 100 cc. The urine contained a moderate amount of calcium, and the sediment showed 10 to 15 white cells per high-power field.

The patient was advised to take 1 glass of milk and 10 drops of viosterol three times a day. She was seen at about yearly intervals thereafter. The blood-chemistry findings at these visits are given in Figure 9 and Table 2. In November, 1941, a urine examination showed a specific gravity of 1.030, no albumin, a moderate amount of calcium and 20 to 30 red cells and 4 to 6 white cells per high-power field. At that time the milk intake was reduced to 2 glasses a day and the viosterol intake was decreased to 10 drops twice a day. In addition, sodium citrate, 2 gm. three times a day, was prescribed.

On November 19, 1942, the urine showed a specific gravity of 1.002, no albumin and 2 red cells and 4 white cells per high-power field. The serum calcium was 10.4 mg. per 100 cc., the serum phosphorus 4.0 mg. and the serum phosphatase 28.0 Bodansky units.

On December 28, the patient slipped on the floor and fractured her right femur at the junction of the middle and distal third. She was admitted to the Baker Memorial Hospital under the care of Dr. George W. Van Gorder.* X-ray examination showed the fracture fragments to be in satisfactory alignment; hence no orthopedic procedures were instituted except simple traction (Fig. 7*B*).

The course thereafter is shown in Figure 9 and Table 2. Because of the experience in Case 1, milk was omitted from the diet from the time of admission, and other fluids by mouth were forced so far as possible. The patient remained comfortable for the first 3 weeks. Then, as the serum calcium began to rise, she complained of anorexia and dryness in the nose and throat, with difficulty in swallowing. This was followed by constant nausea and vomiting. The fluid intake became inadequate. For the next 3 weeks, during the period of maximal hypercalcemia, the patient was given almost daily an intravenous infusion of 1000 to 2000 cc. of equal parts of 5 per cent dextrose and normal saline solutions. On February 8, 1943, when the serum calcium level had fallen to 11.1 mg. per 100 cc., the intravenous infusions were discontinued. At the same time the gastric and pharyngeal symptoms practically disappeared, and thereafter the patient was able to maintain an adequate fluid intake by mouth.

X-ray films taken on January 18, 1943 (Fig. 7*C*), 21 days after the fracture, showed that the alignment had been maintained and that a marked amount of calcified callus was already present. The bone healed so rapidly that by the first week in February the traction could be removed, and by February 15 the patient was able to get out of bed. The subsequent course was uneventful.

DISCUSSION

Pathologic Physiology of Paget's Disease

The pathologic lesions of Paget's disease have been discussed; it remains to attempt an interpretation. It is clear that the initial lesion is a localized factor causing bone destruction, which has no respect for structural requirements. The bone destruction renders the involved bone more susceptible to stresses and strains. To compensate for this, the osteoblasts are stimulated to lay down more matrix; the serum phosphatase level — an index of osteoblastic activity — therefore rises. When the stresses and strains are constantly present (in the vertebras and long bones), bone repair occurs almost simultaneously with bone destruction; when stresses and strains are minimal, as in the skull, bone repair may lag behind bone destruction (see above).

In the meantime, the localized destructive factor persists and continues to destroy bone, including some that has been newly laid down as a reparative process. The joints between new and old bone are

*We are indebted to Dr. Van Gorder for his co-operation in the study of this patient.

TABLE 2. *Chemical Determinations in Case 2.*

DATE	BLOOD SERUM LEVELS					URINE				REMARKS
	CALCIUM	PHOSPHORUS	PHOSPHATASE	PROTEIN	NONPROTEIN NITROGEN	CALCIUM QUASI-QUANTITATIVE TEST*	CALCIUM QUANTITATIVE TEST	SPECIFIC GRAVITY	17 KETOSTEROIDS	
	mg./100 cc.	*mg./100 cc.*	*Bodansky units*	*mg./100 cc.*	*mg./100 cc.*		*mg./24 hr.*		*mg./24 hr.*	
6/ 3/39	10.0	—	—	—	—	++	—	—	—	Classic Paget's disease; 3 glasses of milk and 30 drops of viosterol given daily.
11/18/40	10.4	4.2	42.2	—	—	—	—	—	—	
11/ 5/41	—	3.8	36.2	—	—	++	—	1.030	—	Increased bowing of femurs; sodium citrate, 6 gm. daily.
11/19/42	10.4	4.0	28.0	—	—	—	—	1.002	—	
12/28/42	—	—	—	—	—	—	—	—	—	Fracture, leg in traction; milk stopped and water forced.
12/30/42	10.1	3.7	41.9	5.9	—	—	—	1.024		No complaints
12/31/42	—	—	—	—	—	—	—	1.020	1.7	No complaints
1/ 6/43	11.5	5.5	24.4	4.7	—	++++	—	1.009	—	No complaints
1/11/43	11.9	4.1	31.4	8.0	—	—	—	1.015	—	Anorexia and dysphagia
1/18/43	13.9	4.2	18.8	—	43	++++	434	1.016	2.3	Nausea and vomiting; fluids given by vein.
1/22/43	13.5	3.4	13.4	—	33	++++	—	1.012	3.9	Nausea and vomiting; fluids given by vein.
1/26/43	13.9	3.6	13.3	—	—	—	—	—	—	Nausea and vomiting; fluids given by vein.
2/ 1/43	13.0	4.0	16.5	5.7	—	—	519	1.010	2.9	Patient somewhat better
2/ 8/43	11.1	3.4	16.9	—	—	++	296	1.018	5.6	Intravenous infusions stopped
2/15/43	11.6	3.9	20.1	5.4	—	—	—	1.010	3.2	Patient much better
2/23/43	10.4	3.0	21.4	—	—	+	112	1.010	2.5	No complaints
3/ 1/43	10.7	4.1	31.4	6.7	—	++	—	—	3.2	Traction removed; patient up in chair.
3/ 8/43	9.9	3.2	24.6	6.1	14	0	—	1.027	5.5	Improvement continuing
3/15/43	10.7	3.8	34.8	6.1	18	++	—	1.008	5.5	Patient walked a few steps with brace
3/22/43	9.4	3.5	35.5	7.1	16	+	38	1.006	4.6	Improvement continuing
3/29/43	11.5	3.5	41.5	8.2	22	+	—	—	—	Activity increasing; patient discharged.

*Sulkowitch test.

marked by cement lines; in the constant battle between bone destruction and bone repair many such lines arise. Since the local destructive factor has no respect for the mechanical requirements of the skeleton, the lines have no order, hence the mosaic structure (see arrows in Fig. 2*A*). There results a bone of poor architectural value. This factor explains three of the striking clinical characteristics of the disease: the marked tendency to overgrowth of bone, the fact that the serum phosphatase level, — an index of bone repair, — is so high per unit of diseased bone and the tendency of bones to become deformed in spite of marked overgrowth — for example, bowed femurs.

In Figure 10 the sequence of events is illustrated schematically.

Effect of Immobilization on Paget's Disease

When a bone containing Paget's disease is immobilized, the stimulus for bone formation ceases; and bone destruction continues unabated. There results a decrease in the serum phosphatase level and in bone mass and an increase in the urinary excretion of calcium (Fig. 10*B*). There may even be hypercalcemia when the amount of calcium to be excreted exceeds the ability of the kidney to excrete it (Fig. 9) or when the kidney function becomes impaired from hypercalciuria. Thus, both patients herein cited showed hypercalcemia and some evidence of decreased renal function.

Case 2 illustrates well the sequelae of immobilization in a patient with Paget's disease. The serum phosphatase fell from 42 to a low of 13 Bodansky units; the serum calcium gradually climbed from 10.1 to a high of 13.9 mg. per 100 cc., this high point coinciding with the low point on the phosphatase curve. The daily calcium excretion in the urine reached 519 mg. When activity was resumed the values returned to the prefracture levels, the daily calcium excretion in the urine falling to 38 mg.

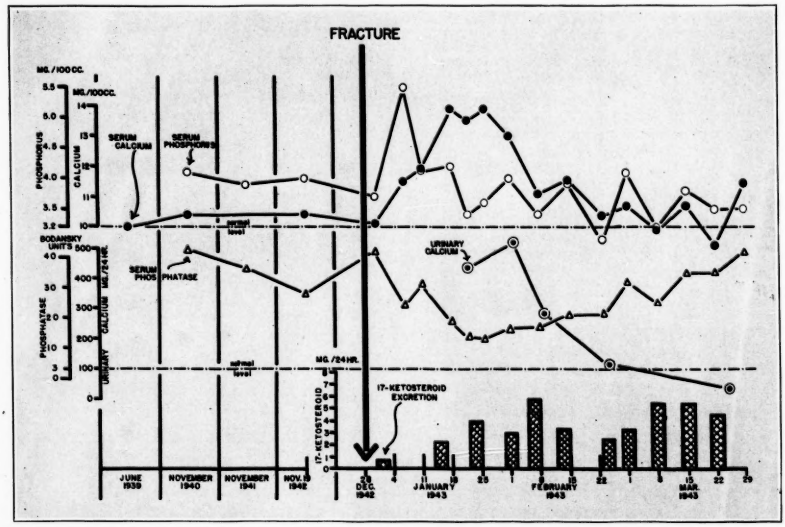

FIGURE 9. *Chart Illustrating the Effect of Fracture on the Serum Calcium, Phosphorus and Phosphatase Levels and on the Urinary Excretion of Calcium and 17-Ketosteroids in Paget's Disease (Case 2).*

In Case 2 there was a depression of the urinary 17-ketosteroid excretion, with a return to a normal value for a patient of this age with recovery — from 1.7 mg. in twenty-four hours on the third day after injury to 5.5 mg. on the seventy-seventh day. It is quite probable that not only this change in the 17-ketosteroid excretion but also part of the depression in bone formation are to be attributed to an alteration of adrenocortical function that is common to all injuries (compare the so-called "alarm reaction" of Selye[8]). The net result of this altered function following injury is a

Possible Role of the Alarm Reaction

curtailment of tissue formation except at the site of injury.[5] Ordinarily such a curtailment may be overlooked, but in Paget's disease, where bone formation is rapid and extensive, any influence that suppresses it is magnified.

It should be noted that this curtailment of tissue anabolism following injuries does not affect the anabolism at the site of the injury. It is not unlikely that there is some local factor that causes maximal tissue repair there. Thus in Case 2, while the rest of the femur was melting away, a good callus was being put down at the site of the injury.

Dangers and Their Prevention

When a patient with Paget's disease is immobilized, the danger of a so-called "chemical death" exists. Thus, the patient in Case 2, if treated in the ordinary fashion with liberal amounts of milk, no special regard for fluid intake and more than minimal immobilization, might well have developed an even higher blood calcium level, anuria and

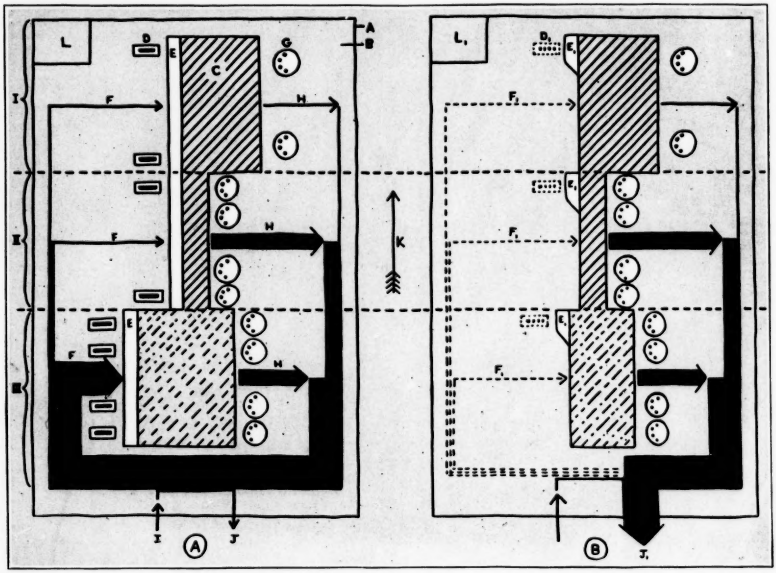

FIGURE 10. *Schematic Diagrams Showing the Processes in Uncomplicated Paget's Disease* (A) *and in Paget's Disease after Immobilization* (B).

Three stages or zones are depicted: I, *normal bone;* II, *bone destruction;* III, *bone destruction with compensatory repair.*

UNCOMPLICATED PAGET'S DISEASE. The designations are as follows: A — *body limits;* B — *body fluid;* C — *bone mass having three surfaces (one where nothing is happening, one where bone is being resorbed, and one where it is being laid down);* D — *osteoblast laying down a matrix of osteoid tissue* (E); F — *arrow indicating by its size the rate of deposition of calcium and phosphorus;* G — *osteoclast;* H — *arrow indicating by its size the rate of resorption of calcium and phosphorus;* I — *calcium and phosphorus entering the body through the gastrointestinal tract;* J — *calcium and phosphorus leaving the body by the kidneys and other exits;* K — *arrow indicating the direction of advancement of the disease process. In Zone* II, *note the decrease of the bone mass, the increase of osteoclasts and the increase in the rate of resorption of calcium and phosphorus. In Zone* III, *note that the increased stresses and strains from the decreased bone mass in Zone* II *have resulted in an increase of osteoblasts, an increase in the rate of deposition of calcium and phosphorus and an increase in bone mass, which is of poor quality. Analyses of the serum* (L) *show a normal calcium level, a slightly elevated phosphorus level and a markedly elevated phosphatase level.*

PAGET'S DISEASE AFTER IMMOBILIZATION. The osteoblasts (D_1) *are hypoplastic owing to loss of the stimulus of stresses and strains through immobilization; this results in a decrease of matrix* (E_1) *and a decrease in the deposition of calcium and phosphorus* (F_1). *In Zone* III *note that the huge amount of compensatory bone formation* (F) *is no longer present because of immobilization. Since bone destruction* (H) *continues unabated, there results not only a marked diminution of the bone mass* (C) *but also a tremendous increase in the excretion of calcium and phosphorus in the urine* (J_1). *Analyses of the serum* (L_1) *show a markedly elevated calcium level, a slightly elevated phosphorus level and a phosphatase level that is still slightly elevated.*

death. Metastatic calcification in the lungs might have been overlooked at autopsy and the cause of death put down as bronchopneumonia. To control the hypercalcemia and hypercalciuria, all that is needed is a low-calcium diet and sufficient fluid by vein if need be so that the serum and urinary calcium concentrations do not rise to dangerous levels. Immobilization should be kept at the absolute minimum, and mobilization should be begun as early as possible, not only to avoid chemical death but to avoid extreme atrophy of the bones (Fig. 5*C*).

A Possible New Symptom of Hypercalcemia

Besides nausea and vomiting, which are recognized symptoms of hypercalcemia, both the patients herein cited experienced a peculiar sensation of dryness in the nose and throat, with difficulty in swallowing. These symptoms seemed to be associated with the hypercalcemia. The patient in Case 1 was treated for "sinusitis" for several weeks before the probable role of the hypercalcemia in producing these symptoms was appreciated.

Summary and Conclusions

The bone lesions of Paget's disease are not generalized but spotty in their distribution. This fact alone is strong evidence against the disturbance being on an endocrinologic or metabolic basis.

The initial lesion in Paget's disease is bone destruction, the cause of this being entirely obscure. The resultant weakness of the involved bones renders them less resistant to stresses and strains, and this leads to a stimulation of the osteoblasts and an overproduction of bone. In the skull, where there are fewer stresses and strains, one frequently encounters bone destruction divorced from the overproduction of bone (so-called "acute Paget's disease of the skull").

The repair of bone by the osteoblasts is never completed, since the localized initial disorder causing bone destruction apparently persists. There results alternating destruction and repair of bone, which eventually leads to the pathognomonic pathological finding, the so-called "mosaic structure." This mosaic appearance is due to the highly irregular cement lines, each one of which demarcates a place where bone destruction temporarily ceased and bone repair began.

The increased bone destruction and bone repair seen in the lesions of Paget's disease are closely similar to those seen throughout the skeleton in the osteitis fibrosa generalisata of hyperparathyroidism. There is one important difference, however: in osteitis fibrosa generalisata, that bone is destroyed that can best be spared; in Paget's disease, bone is destroyed without regard to structure. This accounts for the complete lack of arrangement in the cement lines (see above), and for the fact that the bones in Paget's disease are extremely pliable in spite of marked overgrowth of bone.

If a bone containing Paget's disease is immobilized as after a fracture, the following events occur: A lack of stress and strain, in all probability abetted by the alarm reaction of Selye, curbs the overactivity of the osteoblasts, and the serum phosphatase level, an index of bone formation, falls. The initial disturbance causing bone destruction persists. There results a marked imbalance between bone destruction and bone formation. The increased calcium and phosphorus coming from the bone leads to hypercalciuria and hyperphosphaturia. The capacity of the kidney to excrete calcium may be overtaxed, with a resulting hypercalcemia; if fluids are not forced, if the diet is not kept low in calcium and if immobilization is not kept at a minimum, a so-called "chemical death" from hypercalcemia may supervene.

Studies are cited of 2 patients with Paget's disease who sustained fractures. The above chain of events, up to and including the hypercalcemic stage, took place.

Although, in Paget's disease, the broken bone becomes decalcified as a whole, the fracture site shows a rapidly forming and calcifying callus. This is best explained by the hypothesis that some local influence stimulating osteoblasts is set loose at the site of the fracture.

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EOSINOPHILIC INFILTRATION OF THE LUNGS (LOEFFLER'S SYNDROME)*

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IN the differential diagnosis of pulmonary disease Loeffler's syndrome should be remembered. It has been mistaken for tuberculosis,[1] bronchiectasis and neoplasm, and probably explains many so-

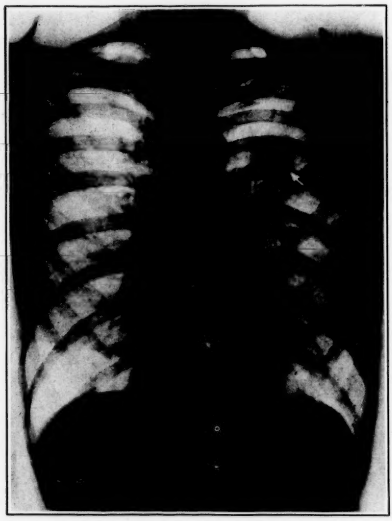

FIGURE 1. *Roentgenogram of Chest Taken October 21.*

called "abortive" pneumonias, as well as the frequent infiltrations seen in roentgenograms of the lungs of patients with bronchial asthma.

Loeffler[2] first described this condition in 1932 and presented 37 cases. Since then a small number of cases has been reported, both in children and in adults, by various authors in many languages. A recent fluoroscopic examination of 6283 men discharged from Army service revealed abnormalities of the lungs in 55.[3] In 13 of these the diagnosis was eosinophilic infiltration.

CASE REPORT

A 33-year-old, married Negress came to the Lahey Clinic on October 21, 1943, complaining of cough and fatigue. She had always lived in the vicinity of Boston, and worked as a private secretary. The cough had been present for 2 weeks and the fatigue for 2 months. The cough was only slightly productive, was worse at night than in the daytime, and was associated with sufficient wheezing so that ephedrine had been prescribed. At times she had a sharp pain of short duration in the right side of the lower thorax, and a "tired feeling" in the lumbar region. She had had similar, but milder, attacks each autumn for the preceding 2 years, but had not felt ill enough to consult a physician.

On physical examination the patient was found to be underweight but did not appear to be ill. The only significant signs were in the upper lobe of the left lung, where the resonance was impaired and sibilant rales were present.

Roentgenograms of the chest showed an infiltration extending out from a large left hilar shadow into the mid-lung and reaching the periphery in the second intercostal space anteriorly (Fig. 1). A pneumonic consolidation or neoplasm was suspected. Examination of the lungs by fluoroscopy suggested the possibility of tuberculosis.

Hematologic examination revealed a marked eosinophilia, which with other findings is shown in Table 1. Hemoglobin determinations, red-cell counts and urine analyses were normal. To discover a possible cause of the eosinophilia, the following tests, the reactions to all of which were negative, were done: sputum examination for tubercle bacilli, a patch test with tuberculin, the giving of eighteen inhalant and food allergens endermically, examination of two warm stools for amebae and ova, agglutination tests for brucellosis,

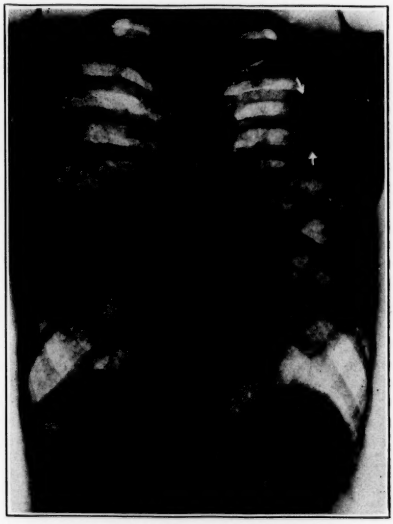

FIGURE 2. *Roentgenogram of Chest Taken October 27.*

and an intracutaneous test with brucellergin (0.1 cc., undiluted), and an intracutaneous test for trichinosis.

The patient continued to rest at home, but was not ill enough to remain in bed. On October 27, a roentgenogram showed some diminution in the lung shadow (Fig. 2), and by December 7 the shadow had completely disappeared (Fig. 3). At that time she no longer coughed, had gained

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3 pounds in weight and felt well enough to return to work. On examination a month later, no abnormal signs or symptoms were present.

Discussion

Since no deaths as a result of Loeffler's syndrome have been reported, the nature of the pathologic

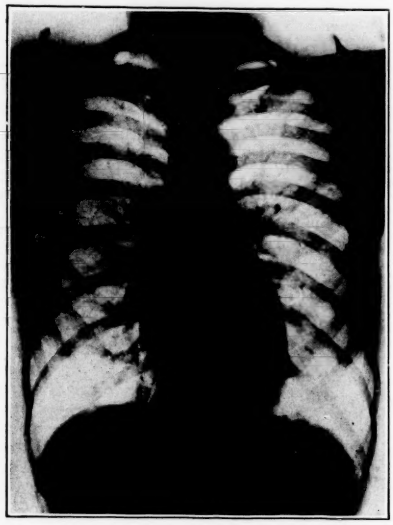

Figure 3. *Roentgenogram of Chest Taken December 7.*

changes that occur in the pulmonary tissues is unknown. Its cause is likewise unknown, although allergy is suspected from its frequent association with vasomotor rhinitis and asthma and its occasional occurrence in persons with an allergic family background. Various substances have been considered as allergens.

In one patient[4] symptoms and roentgenographic findings persisted for four months until amebae were eliminated from the stool. Another patient[5] had amebae in the sputum but not in the stool, and both the lung infiltration and the accompanying asthma disappeared after emetine therapy. Other parasites, such as *Fasciola hepatica* and *Ascaris lumbricoides*, have been found.[4, 6] A seasonal incidence of this disease was recorded in China by Engel[7] who found that cases occurred during May and June while the privet plant was pollinating. Loeffler's cases occurred in July and August. That allergy to the tubercle bacillus may be the cause has been suggested, but Loeffler found positive tuberculin tests in only 13 of 37 adults, and only 1 of these subjects subsequently developed tuberculosis. Smith[8] has reported a case of Loeffler's disease followed by severe asthmatic symptoms.

A possible relation with brucellosis has been suggested in two cases[9] in which there were pulmonary infiltrations accompanied by an eosinophilia and definite evidence of brucellosis.

Eosinophilia thus tends to favor the allergic hypothesis. Ten to 60 per cent of the leukocytes are usually eosinophils, and often the highest count is reached when the infiltration is disappearing. Eosinophilia may persist for variable periods,[10] and in one patient lasted for nine months. There is no parallelism between the degree of pulmonary infiltration and the eosinophil count. Eosinophilia is not essential for making the diagnosis, since it may be absent or be depressed by associated infection. More important for diagnosis are concomitant allergic manifestations.

The patient frequently complains of a metallic taste, cough, wheezing and malaise. He does not feel or appear ill. The temperature may be slightly elevated; diminished resonance with sibilant rales may be heard over the areas of consolidation, and blood examination may show leukocytosis, eosinophilia and an increased rate of sedimentation of the erythrocytes. In contrast to the paucity of signs and symptoms are the roentgenographic changes.

Breton[12] described the shadows in the roentgenograms of the lungs as appearing rapidly, disappearing in three to eight days and reappearing elsewhere in the lungs. Fine star-shaped scars were said to result. Loeffler[1] observed the pulmonary densities to be single or multiple, unilateral or bilateral, and clearly or irregularly outlined, and in some cases to be indistinguishable from pulmonary tuberculosis.

Table 1. *Summary of Data.*

Date	White-Cell Count	Differential Count						Sedimentation Rate
		Eosinophils	Neutrophils	Band forms	Lymphocytes	Monocytes	Basophils	
	x10³	%	%	%	%	%	%	*mm. per hr.*
10/21/43	10,350	48.5	33.0	1.0	13.0	3.5	1.0	31.0
10/27/43	10,150	—	—	—	—	—	—	42.0
11/18/43	8,400	27.0	48.5	0.5	20.0	4.0	0.0	—
12/ 6/43	6,500	9.0	57.0	0.0	31.0	3.0	0.0	8.0
1/ 5/44	6,300	9.0	41.0	0.0	40.0	10.0	0.0	15.0

Summary

A case of Loeffler's syndrome has been presented with a discussion of its significance, cause, symp-

toms and diagnosis. As possible causes the following were considered and rejected: tuberculosis, infestation with amebae or other intestinal parasite, brucellosis and trichinosis. The syndrome appears to be a manifestation of allergy, the cause of which is unknown.

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PENICILLIN SODIUM THERAPY IN EXPERIMENTAL WEIL'S DISEASE*

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REPORTS from different sources [1-3] have conclusively shown the value of penicillin in the treatment of relapsing fever and rat-bite fever in animals. Its remarkable therapeutic value in these two spirochetal diseases suggested that similar action of the drug could be expected in the treatment of infectious jaundice. The following experiments were performed to gain information on this question.

Our strain of *Leptospira icterohaemorrhagiae* was obtained in January, 1944, from Dr. Martin Frobisher of the Johns Hopkins University School of Hygiene and Public Health. It had been freshly isolated from a human infection and was highly virulent for guinea pigs. Prior to the present experiments it was maintained for several weeks in our laboratory by passage in guinea pigs. The infected animals usually developed jaundice on the fourth to the sixth day and died before the seventh day after infection. White guinea pigs, weighing approximately 180 gm. each, were used for the tests. The penicillin sodium was furnished by Dr. Chester S. Keefer. Two experiments were performed.

Experiment 1. Ten guinea pigs were inoculated intraperitoneally with 1 cc. of a suspension of macerated livers and kidneys from other infected animals. Dark-field examinations showed the inoculum to be rich with spirochetes. On the fourth day after infection the entire lot showed varying degrees of jaundice. Five animals in which jaundice was particularly pronounced were selected for treatment. The remaining 5 guinea pigs served as controls. The treated animals received intraperitoneally 4000 Oxford units of penicillin in 1 cc. of saline solution every four hours for seventy-eight hours, or until death occurred.

The first death was that of one of the treated guinea pigs, which had received 4000 units of penicillin. Two more of the treated animals died after having received 8000 units of the drug, and the remaining 2 treated animals were found dead on the morning following the last treatment or after having received the total dose of 48,000 units. All the untreated controls died prior to the death of the 2 guinea pigs that received 48,000 units of the drug. At autopsy, both treated and untreated animals showed similar and characteristic lesions, with motile leptospira in fresh preparations of the liver and kidneys.

From the results obtained from this experiment it appeared that either penicillin was inactive against *L. icterohaemorrhagiae* or that the disease had progressed to such an extent before treatment was begun that any action the drug might have had against the organism did not alter the course of the disease.

Experiment 2. Eight guinea pigs were inoculated with *L. icterohaemorrhagiae*, as in the previous experiment, but treatment was begun before objective symptoms of the disease became apparent. Thirty-eight hours after the inoculations were made, treatment of 4 of the animals was instituted. Each of the treated animals received intraperitoneally 5000 units of penicillin sodium in 1 cc. of saline solution every four hours for forty-eight hours. The total dose received by each guinea pig was 60,000 units.

Jaundice was evident on the third day of infection in all the untreated controls. Three of the controls died, one on the third and two on the seventh day after inoculation. At autopsy these animals showed characteristic lesions of Weil's disease. The fourth control, which appeared to have recovered, was sacrificed on the fifteenth day after inoculation. The internal organs appeared normal. No spirochetes were found in several fresh specimens of the liver, lungs and spleen, but a few were seen in preparations of the kidneys.

None of the treated animals developed apparent jaundice or other signs of illness except slight roughness of fur. One of the animals was found dead on the morning of the fourth day after completion of the treatment. Another was found dead on the fifth day, and a third died on the seventh day after final treatment. Thus, deaths among the treated lot of guinea pigs occurred on the eighth, ninth and eleventh days after inoculation. At autopsy *L. icterohaemorrhagiae* was demonstrated in the liver and kidneys of each of these guinea pigs, but there were no severe lesions. The roughness of fur on the last guinea pig was of a transient nature, and by the tenth day after inoculation it appeared normal. It was sacrificed on the eleventh day after final treatment, or the fifteenth day after infection. All organs appeared normal. No spirochetes were seen in several fresh preparations of the liver, kidney, lungs and spleen.

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In this experiment there is evidence that penicillin had some suppressive effect but was not curative.

The results of a series of experiments by Hamre et al.[4] show that the acute toxicity of penicillin in guinea pigs, mice and rabbits is low; however, daily dosages of 7000 to 12,000 units per kilogram of body weight given subcutaneously over a period of several days caused the death of guinea pigs but not that of mice or rabbits. When guinea pigs were treated with the same dose of penicillin per kilogram as that given to man, they did not die and failed to show any signs of toxicity. It is therefore possible that the death of the treated guinea pigs was due to toxicity of the drug rather than to the experimental infection. The fact that the treated animals in the second experiment did not die until four to seven days after treatment had been stopped indicates that the drug was not the cause of death.

* * *

Our findings are not in accord with those of Heilman and Herrell,[5] who report no deaths from the disease in 32 guinea pigs treated with penicillin and a mortality rate of 91 per cent in an equal number of untreated controls. This difference may be attributed to the early administration of penicillin — seventeen to twenty-four hours after inoculation — and to the use of a strain of *L. icterohaemorrhagiae* with relatively low virulence.

From these results it is apparent that penicillin has a suppressive effect on the organism in a highly susceptible host when given before the appearance of clinical manifestations. This observation suggests that the early use of penicillin might alleviate the symptoms of Weil's disease in man, in whom the disease has a relatively low fatality rate. The value of penicillin in practice, however, is questioned. Its early administration might be effective in preventing the disease, but in the present experiments, it had no curative value after the appearance of clinical manifestations.

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Correction. In the article "Phenarsine Hydrochloride in the Treatment of Syphilis" by Drs. W. F. Boardman and R. Kaldeck, which appeared in the January 6, 1944, issue of the *Journal*, the figures given in Table 2 for the dosage of phenarsine are erroneous. The "thousands" represent the number of doses, and the "hundreds" the dosage in milligrams. In other words, in Case 1 six doses totaling 200 mg. were given, in Case 2, seven doses totaling 300 mg. and so forth.

MEDICAL PROGRESS

THORACIC SURGERY

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THE publication of this review during the sixth year of the war finds many of the world's outstanding thoracic surgeons in the armed forces of their respective countries, and an increasing proportion of a diminishing literature concerned with the surgery of trauma and of war.

Surgery has been called the child of trauma, and it is generally considered that the experiences gained in World War I furnished the impetus that resulted in the precocious development of thoracic surgery, the youngest child of surgery, during the ensuing quarter of a century. Undoubtedly much that will be learned of the surgery of trauma of the chest in this war will be valuable in the highly mechanized peacetime that lies ahead. Even now, for example, there is a better understanding of the principles involved in the treatment of so commonplace a complication as traumatic hemothorax and its sequelae.

There remains, however, a considerable body of literature that deals with the problems of civilian practice, many of which, as is the case in pulmonary tuberculosis, will be greatly augmented by the ravages of war. Other problems, such as bronchogenic carcinoma, are of increasing importance, simply because they are integrated with the natural history of the human race. It is with these and other similar aspects of thoracic surgery that this review concerns itself.

TUBERCULOSIS

Lobectomy

Within very recent years, and with the perfection of the technics of lobectomy and pneumonectomy, many thoracic surgeons who deal with pulmonary tuberculosis have manifested a renewed interest in the application of these procedures to the surgical treatment of this disease.

During the early developmental period of the surgical treatment of phthisis, the actual removal of that portion of a lung containing tuberculous lesions was considered an attractive possibility by various clinicians. Thus, Alexander[1] states that Tuffier performed such an operation in 1891; an indurated tuberculous area in an upper lobe was resected through an incision in the anterior second intercostal space. Seven years later the patient was apparently cured but died of grippe. Up to 1921, however, Tuffier and Jessen had collected less than a dozen cases in which tuberculous pulmonary tissue had been successfully removed, and about as many in which the operation was fatal or otherwise unsuccessful.

In 1935, Freedlander[2] reported a case in which he performed lobectomy for a persistent cavity in the right upper lobe. The patient was alive and well as reported by him[3] in May, 1944. In 1939, Jones and Dolley[4] reported two cases of lobectomy and two pneumonectomies for pulmonary tuberculosis. All the patients survived the operations. These results were considered encouraging. In 1940, Dolley and Jones[5] reviewed their previously reported cases and added 3 more. In the discussion of this paper many surgeons added small series of cases in the aggregate of which the over-all mortality was discouraging. Thus, of 19 patients treated by total pneumonectomy, 8 (40 per cent) died and of 31 treated by lobectomy 8 (26 per cent) died. In 1942, Thornton and Adams[6] collected and analyzed the reported cases of lobectomy and pneumonectomy. There were 29 cases of pneumonectomy with a mortality of 45 per cent and only 41 per cent satisfactory results. There were 46 cases of lobectomy with a mortality of 26 per cent and 69 per cent satisfactory results. It may be presumed that the majority of the operations were performed by the tourniquet technic. In this series, the most frequent complications were persistent fistula, contralateral spread and empyema. The most frequent indications were tuberculoma, tuberculous bronchiectasis, bronchial stenosis and the persistence of a cavity after thoracoplasty.

It is of interest to note that during this period of discouragement, and at the same meeting of the American Association for Thoracic Surgery in 1940 at which Dolley and Jones reviewed their results, Blades and Kent[7] reported 10 successful cases of lobectomy for nontuberculous disease (9 of bronchiectasis and 1 of mixed tumor of the bronchus) in which were employed the technic of intrahilar dissection and individual treatment of each hilar structure of the lobe. This splendid contribution followed closely on the pioneer work of Rienhoff[8] on pneumonectomy for malignant disease by individual ligation and of Crafoord,[9] Churchill,[10] and Churchill and Belsey,[11] the last paper offering new theories of segmental pneumonectomy that had hitherto been only vaguely conceived. It is reasonable to say, then, that a new era in the treatment of pulmonary disease had been entered on.

Up to that time surgical extirpation of the lung or one of its lobes had been accomplished by the use of a tourniquet with mass ligation of the hilar portion of the lung or lobe, as performed by Haight[12] and Graham.[13] Later, after the manner of Shen-

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stone and Janes,[14] who employed a snare threaded with cord to control the hilus of the lobe, the remaining pedicle after amputation of the lobe could be made smaller and hemostasis effected by placing sutures in the presenting cut surface. Shenstone and Janes performed their lobectomies in one stage, as had Brunn[15] in 1929, when he reported 6 cases with 1 death. This technic, although a milestone in the progress of the attack on the problem, was at best unsatisfactory and unsurgical, since it left masses of devitalized and necrotic tissue in the pleural cavity. Moreover, in the case of pulmonary tuberculosis, tuberculous foci were of necessity traversed during the resection of the pulmonary tissue, with the almost inevitable sequelae of tuberculous empyema or bronchopleural fistula and mixed-infection empyema. Frequently the patient was left with a chronic draining chest sinus, secretions from which were often laden with tubercle bacilli. With the spontaneous opening of a bronchopleural fistula during the postoperative course, bronchogenic spread of the disease in the same or the contralateral lung was of a high order of frequency.

With the proved value of the individual ligation technic, the incidence of these hazards was reduced. In most cases it was no longer necessary to transect tuberculous foci or to leave masses of devitalized tissue to serve as a source of infection within the pleural cavity. The hilar vessels could be individually ligated, forestalling postoperative hemorrhage, and the bronchus closed primarily and covered with pleura or buried in surrounding vital tissue, obviating to a large extent the frequently fatal complication of bronchopleural fistula. Moreover, the hilus of the tuberculous lung was found to be relatively free of the fibrosis that is present in suppurative disease, and the intrahilar dissection could be carried out with comparative ease.

In 1943, Churchill and Klopstock[16] reported 6 cases of pulmonary tuberculosis in which modern lobectomy had been performed. All the patients survived the operation and were either well or greatly improved at the time of the publication of the report. These authors make it clear that they propose lobectomy as a highly selective measure for dealing with certain unilobar lesions. They believe it to be far more conservative of pulmonary function than is even a seven-rib thoracoplasty. Since, however, lobectomy is by definition irreversible, it can be suggested as an alternate to artificial pneumothorax only when tuberculosis has produced irreversible or irreparable destruction of lung substance.

In 3 of these cases, lobectomy was performed as a definitive operation where, up to that time, thoracoplasty might have been the operation of choice. In one of the patients, a twenty-two-year-old woman, tuberculin tests (1:50,000 and 1:20,000 dilutions of old tuberculin) were negative one month after operation. In view of the fact that pulmonary tuberculosis is generally considered to have bilateral dissemination, even though microscopic, the implications of such a result could be significant only if many similar cases should be reported and stronger doses of tuberculin be used. Although the total eradication of all foci has been the will-o'-the-wisp pursued by phthisiologists ever since tuberculosis of the lung was recognized as an entity, its accomplishment by surgical means will in most cases probably be purely fortuitous.

At the twenty-fifth annual meeting of the American Association for Thoracic Surgery in May, 1944, several papers were presented that evoked considerable discussion of this important aspect of the surgical treatment of pulmonary tuberculosis. There were many technical issues involved that need not be reported here. Janes[17] analyzed the data in 16 cases of lobectomy that he had performed since September, 1941. The most frequent indication was an open cavity with positive sputum. The upper lobe was affected in 7 cases, the middle lobe in 1, and the lower lobe in 9. Three patients (19 per cent) had died at the time of the report and 13 were considered clinically well. All these operations were performed by the dissection technic. Maier and Klopstock[18] reported on 16 cases of lobectomy for pulmonary tuberculosis. There was 1 death, a mortality of 6 per cent. This death occurred one month postoperatively and was due to a tuberculous spread in the contralateral lung. Of the 15 living patients, 12 had a negative sputum at the time of the report. These authors laid particular stress on the necessity for excellent intratracheal anesthesia, meticulous operative technic and precise localization of the lesions.

Twenty-three cases in which lobectomy was performed — with two operations in 1 case — were analyzed by Overholt and Wilson [19] in a paper read before the 1944 meeting of the American Trudeau Society. There was 1 death, a mortality of 4 per cent. Five patients (21 per cent) had ipsilateral or contralateral spreads or ipsilateral exacerbation of their disease. There were 21 living patients of the 22 whom the authors classified as "reasonable risks"; and in these cases the prognosis was considered good in 13 (62 per cent), guarded in 7 (33 per cent), and poor in 1 (5 per cent).

Although Chamberlain[20] agrees that there is a place for lobectomy in the treatment of pulmonary tuberculosis, he presents his arguments why he believes that modern selective thoracoplasty with its low mortality (2 to 5 per cent) and high rate of sputum conversion (80 per cent) should be the procedure of choice in disease of the upper lobe. He believes that lobectomy should be performed only after failure of thoracoplasty because in his opinion based on bronchospirometric studies, "primary upper lobectomy" excises only the active major focus, thus causing overdistention of the remaining lobe, which is probably a precursor of emphysema,

may cause reactivation of latent foci in the overdistended lobes, and leaves these foci in a poor state of healing or self-protection.

Maier[21] takes issue with this point of view. He has been unable to demonstrate serious impairment of respiratory function of the remaining lobe or lobes by bronchospirometric studies, and believes that true emphysema of functional significance does not occur in the remaining lobe. Apparently progressive lowering of the oxygen-consumption curves does not occur.

It can thus be seen that there is considerable difference of opinion regarding primary upper lobectomy as a definitive operation. Thoracoplasty is an operation of known potential and mortality, whereas there is no imposing array of statistics dealing with lobectomy performed in cases in which, up to now, thoracoplasty might have been considered the operation of choice. Until such time as there is a sufficient number of cases to be of statistical significance, and until enough time — possibly five years — has elapsed to evaluate properly the results — any detailed discussion must be regarded as largely philosophical. Certainly, the use of lobectomy in well-selected cases should be continued. The hazard that the procedure will be carried out indiscriminately to achieve rapidly the prestige of numbers, as has happened all too often in the history of the surgical treatment of tuberculosis, is ever present, and should be guarded against with great fortitude so that the procedure will not be condemned before it has had a carefully controlled trial.

But although at the present time it seems that primary lobectomy of the upper lobe is far from the philosopher's stone in the treatment of pulmonary tuberculosis, there are other indications for lobectomy that appear to be fairly well defined but concerning which there is lack of complete accord among phthisiologists and thoracic surgeons. From my own experience with 14 cases — 7 lobectomies and 7 pneumonectomies — and that of others,[16–19] these indications appear to include tuberculoma, tuberculous bronchiectasis, certain tension cavities, particularly of the lower lobe, stenotic lesions of lobar bronchi and residual cavitation when thoracoplasty has failed.

Pneumonectomy

The problem of pneumonectomy in tuberculosis differs radically from that of lobectomy. Churchill and Klopstock[16] state:

> Total pneumonectomy cannot be considered an alternative to collapse therapy provided that collapse therapy is applicable to the case under consideration. It is both irreversible and nonselective. It irrevocably and seriously limits any therapeutic procedure that may be needed for the lung of the contralateral side. Circumscribed by strict indications, total pneumonectomy in tuberculosis may be a life-saving operation when no other operation is feasible.

Since total pneumonectomy is in most cases performed with greater facility for technical reasons than is lobectomy, there is undoubtedly a tendency to abandon the former, if planned in a given case, and to resort to the latter when the original lobectomy if persevered in might have been successfully completed. This has obscured the issue in many cases and rendered the evaluation of results even more difficult, since the indication for pneumonectomy did not originally exist.

The most frequent indication for total pneumonectomy in tuberculosis is partial or complete stenosis of the main-stem bronchus, with or without symptoms of obstruction as manifested by toxemia. Thus, Lorge and Dufault,[22] reporting 3 cases from the Rutland State Sanatorium, state that in 2 the indication was stenosis of the stem bronchus and that in 1 there was widespread bronchial involvement with clinical evidence of repeated blockage of secretions. There was 1 death, and 1 patient had a not very active lesion in the contralateral lung that appeared six months later but showed evidence of clearing.

Of the 15 total pneumonectomies reported by Janes,[17] 10 were performed for stenosis and in 7 of these there was an uncomplicated recovery. Other indications were tuberculoma, extensive infiltration of the whole lung with cavitation and hemorrhage, and cavitation of the middle lobe with infiltration to the upper and lower lobes. In the total series there were 3 deaths (20 per cent), 10 patients were considered well or fairly well, and in 2 cases the outlook was unfavorable.

In the series of 36 pneumonectomies reported by Overholt and Wilson[19] there were 6 deaths, a mortality of 17 per cent. The authors divide their cases into "desperate risks," of which there were 11 with 5 deaths (45 per cent), and "reasonable risks," of which there were 25 with 2 deaths (8 per cent). In the total series there was a contralateral spread in 4 cases (11 per cent). In 29 of the cases pneumonectomy was performed for extensive multilobar disease that was predominantly unilateral, in 5 for uncontrolled disease following thoracoplasty, in 1 for basal tuberculosis, and in 1 for extensive disease of the upper lobe found at operation to involve the lower lobe as well. There is no detailed analysis of the present status of the entire series, but of the 23 living "reasonable-risk" patients the prognosis was considered good in 18 (78 per cent), guarded in 3 (13 per cent) and poor in 2 (9 per cent).

At the Massachusetts Memorial Hospitals, pneumonectomy has been performed in 7 cases of tuberculosis. The indications were as follows: stenosis of the main bronchus in 2 cases, extensive unilateral disease in which other measures had failed in 3, pneumothorax failure with an unexpansible lung in 1 and pneumothorax failure with the cavity in the lower lobe reopened after three years in 1. There were 3 deaths (43 per cent), all in the group with

extensive unilateral disease, from nontuberculous pneumonia in the remaining lung, surgical shock and extensive tuberculous contralateral spread, respectively.

Alexander[23] states:

> The choice between thoracoplasty and pneumonectomy must be based on a number of important factors. If the bronchial stenosis is so great that the patient cannot effectively evacuate the pulmonary secretions by coughing even after attempted bronchoscopic dilatation of the stricture, and consequently becomes increasingly toxic, thoracoplasty would be unduly dangerous because it probably would, at least during the period of the staged operations, further impair the effectiveness of coughing. In such cases, pneumonectomy is the operation of choice and should also be considered if thoracoplasty has already been performed and has left the patient with the symptoms just mentioned. But if there are any active tuberculous lesions in the opposite lung, or if any progressive ulcerative bronchial lesions are present, pneumonectomy is definitely contraindicated. In this event, no surgical treatment, unless possibly direct surgical drainage of a single large tuberculous cavity, could safely be used. There are very few patients who have the clear-cut indications for pneumonectomy and, at the same time, no contraindication.

This sound opinion is probably the one held by the great majority of thoracic surgeons. Although the presence of bronchial stricture undoubtedly makes thoracoplasty more hazardous, Alexander, Sommer and Ehler[24] report that 25 patients (66 per cent) in a series of 38 cases have closed cavities and negative sputums and that only 3 (8 per cent) are dead.

As is the case in lobectomy, only time and a careful follow-up will permit an accurate evaluation of the place of pneumonectomy in the treatment of pulmonary tuberculosis.

Bronchogenic Carcinoma

The increasing frequency with which cancer of the lung has been reported as a cause of death in recent years has aroused considerable speculation whether the increase represents a real change in the incidence of this form of malignant neoplasm or is merely the result of improved methods of diagnosis in combination with a more careful search for a disease that has attracted attention because it is reported more frequently than it has been in the past. Dorn[25] states that between 1914 and 1930 the death rate from cancer of the lungs and pleura increased by nearly 400 per cent, as compared with an increase of 20 per cent for all forms of cancer combined. The change among males exceeded that among females, the respective increases being 450 and 260 per cent.

The death rate from cancer of the lungs and pleura continued to increase from 1930 to 1940. Eliminating the changes in the age composition during the past decade, this death rate is shown to have increased by 22 per cent among white females and by 78 per cent among white males, or roughly 2.5 and 8.5 per cent per year, respectively. Nearly 3 per cent of 39,970 patients with malignant neoplasm in the white population of a study group were reported to have a primary cancer of the lung.

It is estimated that between 450,000 and 500,000 persons in the United States are under treatment for cancer. In approximately 20,000 of the known cases there is a primary cancer of the respiratory system; of these patients about 13,000 are being treated for primary cancer of the lung. Slightly more than 8000 new cases of primary cancer of the lung are diagnosed and receive treatment for the first time each year.

Ochsner and DeBakey[26] state that at the beginning of this century the lesion was considered a museum curiosity, but that recently it has been shown that the lung ranks second only to the stomach as the primary site of cancer. This statement is in accord with a ten-year survey of autopsies on carcinoma of the lung by Halpert[27] at the Charity Hospital in New Orleans, which reveals both a relative and an absolute increase. During the decade ending December 31, 1940, 12,972 autopsies were performed, 8862 of them on persons over one year of age. Among the subjects there were 135 with carcinoma of the lung, 205 with carcinoma of the stomach, and 66 each with carcinoma of the biliary system and of the pancreas. A year-by-year analysis shows that whereas the incidence of carcinoma of the stomach remained about the same, that of the lung gradually increased and during the last two years *exceeded* that of carcinoma of the stomach.

Blades[28] states that at the Barnes Hospital in St. Louis 62 proved cases of bronchogenic carcinoma were seen from 1933 to 1936. During the following three years, 117 patients with bronchogenic carcinoma were admitted for treatment. It thus becomes apparent that the increase in the incidence cannot be attributed to improvements in diagnosis or increased awareness of the condition, but must be considered actual, as demonstrated both by autopsy and by clinical observations.

Although bronchogenic carcinoma occurs most frequently in the age group of fifty to seventy, no age is exempt. It is seen frequently in the thirties and forties, and Hauser[29] reports a case in a Negro baby aged seventeen months.

To my knowledge, there has never been an authenticated case of bronchogenic cancer that has been reported as a five-year cure as the result of radiation therapy. Many radiologists,[30, 31] however, believe that this form of therapy has palliative usefulness and should be employed in certain inoperable cases.

It is now generally recognized that the ideal in the treatment of bronchogenic carcinoma is its surgical extirpation by total pneumonectomy. In rare cases lobectomy may be used, but, as in cancer surgery in general, only by the sacrifice of the entire organ can one hope to achieve the greatest number of cures. Since Graham's[13] first successful

case in 1933, hundreds of successful pneumonectomies have been performed in the various thoracic clinics throughout the world.

Unfortunately, the vast majority of cases in which this diagnosis is made are inoperable when first seen by the thoracic surgeon. Thus, of 155 cases of primary carcinoma of the lung seen by Churchill[32] only 27 (17 per cent) were suitable for resection. In a recent three-week period, I saw 18 patients with proved bronchogenic cancers, only 1 of whom was operable when first seen and on whom pneumonectomy was successfully performed. During 1941 to 1943, approximately 75 cases were diagnosed and 50 proved histologically at the Boston City Hospital and Massachusetts Memorial Hospitals. Of these only 7 (9 per cent) were operable. Overholt[33] found 26 per cent of his cases to be operable. It may therefore be assumed that somewhere between 10 and 25 per cent of cases are operable when first considered for surgery, a sad reflection on the ability of physicians to recognize this relatively frequent disease in its early and favorable stages.

The contraindications for pneumonectomy, which in most cases constitute the reasons for inoperability and as a corollary mean a late diagnosis and advanced disease, are based on certain findings. These have been summarized by Graham[34] as follows:

The presence of bloody pleural fluid. This usually means invasion of the visceral and parietal pleura by the growth. In most cases, the presence of clear effusions also means inoperability, and the finding of tumor cells in such effusions makes it certain.

Paralysis of the corresponding half of the diaphragm, as determined by fluoroscopic examination. This usually is evidence of invasion of the phrenic nerve.

Paralysis of the left vocal cord in cases of left-sided bronchogenic carcinoma. This usually denotes invasion of the left recurrent nerve as it passes under the arch of the aorta.

Severe pain in the thoracic wall or down the arm. This is a bad sign and generally is evidence of an involvement of intercostal nerves or of the brachial plexus. The presence of a moderate amount of pain, however, should not preclude an exploratory operation.

Bronchoscopic evidence of extension of the tumor into the trachea. This usually contraindicates pneumonectomy, although occasionally it is possible to remove even a part of the wall of the trachea.

The presence of distant metastases. In exceptional cases it may prove justifiable to remove both the lung and a solitary metastasis.

The question of the age of the patient is important from the standpoint of operability, but at least up to the present time there is no fixed limit. The general condition, and particularly that of the cardiovascular apparatus is more important than the chronological age. (Graham's oldest patient to survive was sixty-eight; another patient of seventy years made an immediately satisfactory recovery but died suddenly of coronary thrombosis one week later.)

In view of the frequency of the occurrence of the disease and its insidious character in the early stages, only a concerted effort, together with the acquisition of a nation-wide state of awareness to bronchogenic cancer on the part of the medical profession as a whole, will result in early diagnosis for a greater number of patients afflicted with this disease and a consequent improvement of the chances for cure.

Any male patient of middle age or beyond who develops cough and expectoration, with or without hemoptysis or blood streaking, and who cannot be shown to have tubercle bacilli in the sputum should be considered to have bronchogenic carcinoma until it is proved unequivocally that there is some other reason for his symptoms.

The first step leading to diagnosis is, of course, a roentgenogram of the chest. In most cases this simple procedure suggests the diagnosis either by indirect evidence, such as atelectasis of a lobe or lobes due to an obstructive bronchial lesion, or by the more positive evidence of an infiltrative hilar lesion or parenchymal tumor. Alexander[35] states that despite the prevailing impression, most *circumscribed* intrathoracic neoplasms are intrapulmonary and malignant. All pulmonary abscesses and suppurative lesions should be considered as resulting from bronchogenic carcinoma. In general, one may say that the roentgenogram shows the tumor, which may be relatively tiny, less frequently than its result, which usually predominates in the clinical picture. In rare cases the roentgenogram is negative. In any event, the second step is almost always bronchoscopy, by which a positive diagnosis before operation can best be made. In Graham's[34] experience a positive diagnosis can be made by bronchoscopic biopsy in about 75 per cent of cases. Holinger and Radner[36] state that in Jackson's series a diagnosis by biopsy was possible in 75 per cent of cases of bronchial cancer, and that Kramer and Som obtained a positive tissue diagnosis in 74 per cent of cases and Clerf in 68 per cent.

The problem of what advice to give in the 25 per cent of cases without a positive diagnosis is an important one. In Graham's[34] opinion, the answer is generally fairly simple. If there is a reasonable suspicion of carcinoma, an exploratory thoracotomy should be performed without delay, for in this way many lives can be saved. Too often the advice of the physician has been to wait to see if anything happens. Nothing is gained by this delay, and the usual result is another victim.

An analysis of the risks involved in pneumonectomy reveals an encouraging trend for an operation that must be considered to be technically still in its

developmental stage. In 1940, seven years after the first successful pneumonectomy for bronchogenic cancer, Churchill[32] reported hospital deaths in 14 (67 per cent) of 21 patients undergoing total pneumonectomy. Fifteen of the 27 patients subjected to resection — lobectomy and pneumonectomy — died in the hospital, and 7 died subsequently of their disease. At the time of the report, 5 of 155 patients with proved primary carcinoma were alive with no apparent residual or recurrent disease. Churchill finds these results to be similar to those reported by Edwards, who noted a salvage of 6 patients out of a total of 172 cases. In 1940, Samson and Holman[37] reported 5 cases with 4 recoveries, and in the same year, Ochsner and DeBakey[38] reported 19 cases with 10 recoveries. In 1941, Overholt[33] reported 31 cases with 9 operative deaths (29 per cent). Graham[34] reports that in the last 25 cases of pneumonectomy performed by him and Blades there were only 3 deaths, a mortality of 12 per cent.

Graham further discusses the question, Shall the thoracic surgeon offer a chance, even though a small one, to the bad-risk victim of bronchogenic carcinoma, or shall he decline to operate because of the great danger of an operative mortality? He believes that most thoracic surgeons offer the patient a chance of recovery. A mortality of 12 per cent in 25 cases is a respectable one, and should dispel the all too widespread belief that the operation of total pneumonectomy for primary cancer carries with it an enormous operative risk. It should be remembered that without operation the risk is 100 per cent.

Bronchiectasis

It is now generally agreed that the definitive treatment of bronchiectasis is surgical, and that most patients in whom it is discovered should be considered for lobectomy or pneumonectomy, although many may, after evaluation, be denied operation for a variety of reasons.

Corroboration of this statement is obtained in several recent studies, one of the best of which is presented by Perry and King.[39] Basing their conclusions on a follow-up of 400 patients, these authors show that in a twelve-year study the mortality in the nonsurgically treated cases was 26 per cent, 41 per cent of these patients dying within five years of onset and 15 per cent living twenty years or longer after onset. Of the patients who died, 78 per cent died directly from their disease. Some statistical evidence supports the view that patients who develop bronchiectasis before the age of ten do not live beyond the age of forty. Thus, of persons with the onset in the first decade only 9 per cent were living at the age of forty or over. Of the 59 patients who reached the age of forty or over, in only 15 per cent was the onset in the first decade. The operative mortality in one hundred and twenty-two modern-type lobectomies performed on 116 patients (by Churchill at the Massachusetts General Hospital) was 3 per cent. The working and living capacity of the traced living patients was considered to be excellent in 67 per cent of the surgical group and 38 per cent of the nonsurgical group. These authors find nonsurgical treatment to be only palliative and believe that because of the steadily decreasing operative mortality rate, simple lobectomy may be advised without hesitation. Even with bilateral disease the risk in bilateral lobectomy — of course in two stages — is often not too great.

Bradshaw, Putney and Clerf[40] studied 242 patients with bronchiectasis. Of these 112 were living and 59 died from bronchiectasis or its complications.

Riggins[41] found the mortality for 85 patients with medically treated bronchiectasis collected during ten years with many observed for only three or four years, to be 14 per cent. He concludes, "The morbidity and mortality of untreated and medically treated bronchiectasis . . . is such that the physician who routinely advises young adults with operable bronchiectasis against surgery, is assuming a grave responsibility and in all probability renders his patient a great disservice." It should be added that children stand thoracic operations exceptionally well, and lobectomy early in life is almost certain to obviate the hazards of bronchiectasis that such children must face if they grow to adolescence or adult life with nonsurgical treatment.

Averaging the figures given by various students of the disease, Hinshaw and Schmidt[42] estimate that less than 10 per cent of patients with severe bronchiectasis obtain a satisfactory result from any form of medical treatment, and conclude that the mortality rate within ten or fifteen years after the diagnosis is made is somewhere between 30 and 50 per cent. When severe bronchiectasis appears in childhood, it is improbable that the patient will live beyond the age of forty years.

The development of the modern technic[7] of intrahilar dissection and individual ligation has further improved the operation of lobectomy as applied to bronchiectasis. Although occasionally not feasible or even impossible in cases of so-called "frozen hilus" owing to dense fibrosis resulting from repeated exacerbations of pneumonitis, this technic materially reduces the postoperative complications of empyema and bronchopleural fistula already alluded to in the section on lobectomy in tuberculosis. The advent and increasing availability of penicillin promises a further reduction in the incidence of postoperative empyema. At the Massachusetts Memorial and Boston City hospitals it has already been used prophylactically, in a few cases both intrapleurally and intramuscularly, as part of the postoperative routine, with gratifying results. It is still too soon, however, to draw any definite conclusions.

Additions to the knowledge of the surgical anatomy of the detailed structure of the lung, refinements in bronchography and clinical experience have demonstrated that a lobe of the lung is actually made up of a cluster of bronchopulmonary segments. In this connection an important contribution was made by Churchill and Belsey[11] in 1939. They correctly prophesied that the bronchopulmonary segment would replace the lobe as the surgical unit of the lung. Although it had been suggested by Nelson[43] in 1934 that the lungs are made up of eight lobes — two upper lobes, two middle lobes, the dorsal divisions of the lower lobes and the basal divisions of the lower lobes — it remained for these surgeons to demonstrate the actual clinical application of such an anatomic configuration. They applied the principle of segmental pneumonectomy to resection of the lingula of the left upper lobe — left middle lobe — by removing the posteromedial segment of the lingula, and also employed the technic in operations on the dorsal divisions of the lower lobes. In a recent paper, Blades[44] describes a technic for other partial excisions, for example, of the basal division of the lower lobe. He used it satisfactorily in 8 cases, with no deaths. Such contributions are of value since they point the way to greater conservation of normal pulmonary tissue in certain lesions well localized in a bronchovascular segment of the lung.

No discussion of the operative treatment of a disease is complete without reference to the risks involved. Churchill's excellent figures, as reported by Perry and King,[39] have been mentioned. Bradshaw and O'Neill[45] report the results of surgical treatment of bronchiectasis in 76 patients whose disorder was mostly due to an unknown etiologic agent. One death occurred among the 24 patients with disease of the lower lobe and of the lower lobe and lingula, a mortality of 4 per cent. Among 26 patients in whom one lobe was removed but disease was present in other lobes there were 4 deaths, a mortality of 15 per cent. Seventeen patients had two or more lobes removed, with 3 deaths, a mortality of 18 per cent; 11 had disease in other lobes. Maier[46] reports 64 cases in which pulmonary resections for bronchiectasis were performed. Lobectomy was done in 55 cases, and pneumonectomy in 9, with 1 operative death, a mortality of less then 2 per cent.

Bilateral lobectomy, in stages, has frequently been performed for bronchiectasis. It is now considered routinely in planning the surgical program of suitable bilateral cases. Churchill[32] reports 6 cases with 1 death. We have performed bilateral excision in 4 cases with no death. As might be expected, however, and, as is borne out in Bradshaw and O'Neill's[45] figures, bilateral lobectomy is associated with considerably higher mortality, since it subjects the patient to two major operations. Moreover, the postoperative period after the first lobectomy is rendered more hazardous because the patient must convalesce with disease remaining in one or more lobes.

Pseudobronchiectasis

In a communication emphasizing the importance of the effects of atypical pneumonia on the bronchi and the production of pseudobronchiectasis, Blades and Dugan[47] state that 6 patients with almost identical histories have been observed at the Walter Reed Hospital. Bronchograms, following an acute illness diagnosed as atypical pneumonia, demonstrated bronchial dilatations, but after a period of one or two months the configuration of the bronchi returned to normal. The authors therefore believe that atypical pneumonia can produce temporary enlargement of the bronchi, and urge that surgical intervention be delayed in questionable cases until repeated bronchograms and the clinical features of the disease establish an unequivocal diagnosis of anatomic bronchiectasis.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30361

PRESENTATION OF CASE

First admission. A fifty-nine-year-old mechanic was admitted to the hospital because of swelling of the legs and ankles.

The patient had been in excellent health until four months before entry, when he noticed swelling of the ankles and legs, especially at the end of the day. Soon after, he developed exertional dyspnea. He had apparently slept on two pillows all his life and continued to do so without any change. The swelling, however, increased and progressed to involve the scrotum and penis. About two months before entry he gave up his job and was hospitalized in a community hospital for one week. There he was given three pills daily and numerous injections; the nature of these was not known. The swelling of the legs subsided; he felt much better and was discharged to the care of his physician, who continued to give him two injections a week and three capsules daily. Following discharge, however, his symptoms gradually returned. He had had no orthopnea, paroxysmal nocturnal dyspnea, chest pain or palpitation. Edema of the ankles and legs and exertional dyspnea, however, progressed, and the abdomen became slightly larger. His appetite had remained essentially the same.

The past history was negative.

*On leave of absence

Physical examination showed a well-developed, well-nourished man in no discomfort. The left border of cardiac dullness was 4 cm. to the left of the midclavicular line. The rate was slow (48) but regular except for an extrasystole every tenth or fifteenth beat, with compensatory pauses. A loud systolic murmur was heard over the whole precordium but was maximal over the aortic area, accompanied by a questionable systolic thrill. The murmur was well transmitted up the neck vessels. There was a questionable early diastolic murmur to the left of the sternal border. The pulmonic second sound was greater than the aortic. Crackling rales were heard at both bases. The liver edge was palpable two fingerbreadths below the costal margin. Massive pitting peripheral edema, as well as edema of the penis, scrotum and sacrum, was present.

The blood pressure was 145 systolic, 70 diastolic. The temperature was 98.6°F., the pulse 48, and the respirations 22.

Examination of the blood showed a red-cell count of 4,100,000, with 13.4 gm. of hemoglobin. The white-cell count was 9000, with 67 per cent neutrophils. The urine gave a + + test for albumin but was otherwise negative. A Wassermann and two Hinton tests were negative.

The patient was given 4 cc. of Cedilanid and 2.2 cc. of Mercupurin. One half hour later the radial pulse was 27, but he had no subjective symptoms. An electrocardiogram on the following day showed auricular fibrillation with an average rate of 42. The ST_1 and ST_2 waves were depressed, the T_1 and T_2 waves diphasic, and the T_3 waves low. T was inverted in CF_4. The nonprotein nitrogen was 39.5 mg. per 100 cc.

The patient was given 3 gm. (45 gr.) of ammonium chloride daily. An electrocardiogram one day after the first tracing revealed no significant change. On the fourth hospital day he was started on 0.1 gm. (1½ gr.) of digitalis daily and was given 2.2 cc. of Mercupurin intravenously which was repeated two days later. He continued to receive ammonium chloride and digitalis daily and re-

sponded well. On the tenth hospital day examination of the heart revealed slow fibrillation. The sounds were of good quality. There was no deficit. There were dry rales in the lung bases and sticky prolongation of the breath sounds. The edema had cleared except in the left calf, where it was apparently due to marked superficial and deep varicosities. The right calf was relatively unaffected. An x-ray film of the chest on the following day showed gross enlargement of the heart, both to the right and to the left. The transverse diameter of the heart was 19.5 cm., with an internal chest diameter of 34.0 cm. The lung fields were clear. There was no fluid in the costophrenic sinuses.

On the twelfth hospital day, the lungs were clear to auscultation and the patient had no orthopnea or dyspnea. There was no edema except for slight swelling of the left leg. He was discharged home on 0.1 gm. of digitalis and 3 gm. of ammonium chloride daily and a low-salt and low-fluid diet and was advised to remain inactive.

Final admission (seventeen days later). Following discharge the patient did well for one week. At the end of that period he contracted a cold, with rapid recurrence of the previous symptoms of dyspnea and edema. He then experienced increasing orthopnea. His condition progressed rapidly so that in about five days edema had reached the sacrum, involving both legs, the scrotum and the penis. Two weeks after discharge he returned to the Out Patient Department, where the intravenous injection of Mercupurin gave no relief. He was admitted two days later.

Physical examination showed an extremely dyspneic and orthopneic man with an unproductive cough. The heart was slowly fibrillating, with a rate of 60 and without any pulse deficit. The heart was otherwise the same as before. There was fluid in both lung bases, and basal moist rales. The liver edge was palpated seven fingerbreadths below the costal margin. Ascites was present as well as a marked pitting edema of the extremities up to the sacrum.

The blood pressure was 158 systolic, 88 diastolic. The temperature was 96°F., the pulse 70, and the respirations 20.

Examination of the blood showed a red-cell count of 5,020,000, with 11.5 gm. of hemoglobin. The white-cell count was 9200, with 70 per cent neutrophils.

The patient was given intravenous Mercupurin and oral digitalis and ammonium chloride. On the second hospital day he was found to be unable to void; he was catheterized, at which time only 45 cc. of urine could be obtained. This showed a ++ test for albumin, contained white cells and had a pH of 7. He was given 100 cc. of 50 per cent dextrose solution intravenously, followed by 100 cc. of physiologic saline solution, with little, if any, success. He had a great deal of respiratory distress and became slightly cyanotic. The radial pulse rose to 90. The nonprotein nitrogen rose to 203 mg. per 100 cc. He died on the fourth hospital day.

Differential Diagnosis

Dr. C. Sidney Burwell*: I should like to begin by commenting on the electrocardiogram and by seeing the x-ray films.

Dr. Benjamin Castleman: Would you care to see the electrocardiogram?

Dr. Burwell: The fourth lead shows a strikingly inverted T wave. There is an upward wave that I should call an R, and a deep S. The ST_1 and ST_2 waves are depressed, but only slightly so. Fibrillary waves are perfectly apparent. The rate is slow, and it appears to be quite regular. I should place it as a regular rate originating in the ventricles.

In this x-ray film the left border of the heart is not straight, but it is a rather expressionless left border. In the oblique view was the right auricle enlarged?

Dr. Laurence L. Robbins: I do not believe that one can tell, but I presume that the patient was fluoroscoped and that the notation in the record was made from that. In this lateral view it is rather hard to tell whether or not the auricle is enlarged.

Dr. Burwell: It is a big lobular heart in both directions, with enlargement of most of the chambers. Certainly the left ventricle is enlarged, and I suspect that the auricles are dilated.

I find this a complex and difficult case. I should like to discuss briefly three possibilities with regard to the nature of the disease. The first decision I should like to make is whether this patient had heart failure or some other cause for this progressive and recurrent edema and dyspnea, which eventually "did him in." There are several other possibilities. First, one raises the question of whether he had obstruction of the entry of blood into the heart which was on a mechanical obstructive basis rather than because of what we call heart failure. In other words, Did he have constrictive pericarditis or pericardial effusion? I believe that the evidence is strongly against both of them. The cardiac signs did not resemble those commonly observed in either of those situations, and I am content to set that diagnosis aside.

One asks, Did he have mechanical obstruction lower down in the venous system than the right auricle? The point has been made, and with a good deal of force, that the edema started at the feet and rose to the level of the sacrum and no higher. One wonders if that is a suggestion that he had a bilateral obstruction to returning venous circulation from his legs, perhaps on the basis of recurrent thrombosis extending up into the iliac

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system and so on, or perhaps even into the inferior vena cava. He showed no evidence of collateral circulation, which he should have if he had had obstruction to the vena cava for some time. He had a few varicose veins in one leg that seem adequately to account for the extra edema on that side, but I should hesitate to blame the edema on venous obstruction. I am always impressed by the small amount of edema that is brought about by most venous obstruction.

One then asks, Did he have cirrhosis of the liver? To ask the question is to answer it in the negative, I believe. The same can be said of nephritis.

I am reasonably satisfied to conclude that the first item in this patient's diagnoses is heart failure, and I am comforted in that conclusion by the fact that he had certain findings that ordinarily go with congestive heart failure. He had a large heart, for example, and evidence of various kinds of cardiac disease. I shall accept heart failure as the first diagnosis.

The second decision concerns the nature of his cardiac disease, and here I find the going a good deal stormier. In the first place, the evidence is not altogether conclusive. If one sees a man of this age with a large heart, which this man certainly had, with a loud systolic murmur (I think this was loud for two reasons: the record says it was, and it was heard in the vessels of the neck) accompanied by a thrill and a diastolic murmur, one can be reasonably well advised to conclude that he has aortic stenosis. Aortic stenosis is no rare disorder. It is particularly common in men of this age. It is compatible with many years of continued good health and also compatible with a short and progressive period of cardiac failure leading to death from cardiac failure. One's confidence, however, in that diagnosis is rudely shaken by the word "questionable," which is attached to the most important sign. The best evidence of aortic stenosis is an unquestioned aortic thrill. Another almost incontrovertible evidence is the demonstration of calcium in the aortic valve. I cannot see calcium, but it usually is not seen in the film. Was it seen on fluoroscopy?

DR. ROBBINS: I doubt it.

DR. BURWELL: Is there any note to that effect?

DR. CASTLEMAN: No.

DR. BURWELL: So we do not have incontrovertible evidence of calcium or the definite evidence of a thrill. My impression of aortic stenosis is further shaken by the question mark put after the diastolic murmur. It is always comforting to have an aortic diastolic murmur. Most people with loud diastolic murmurs have heart disease, and even a higher percentage of people with diastolic murmurs have heart disease. Most people with early diastolic murmurs at the left sternal border have aortic regurgitation. If a man has aortic regurgitation he almost always has disease of the aortic valve. The diagnosis of aortic stenosis is often made on the demonstration of aortic insufficiency. This man's blood pressure is quite compatible with aortic stenosis and regurgitation. He apparently did not have a greatly elevated peripheral blood pressure, but he did have a wide pulse, which tends to support the existence of this questionable diastolic murmur. On the other hand, one cannot lean too heavily on that for several reasons. In the first place, diastolic pressures are often variable or misleading. In the second place, a person with a slow pulse rate usually has a relatively wide pulse pressure for obvious reasons; it is a long time between systoles and the diastolic pressure has that much more time to fall. So I find myself in grave uncertainty whether or not this mass had an aortic regurgitation, but it does appear that he had aortic stenosis. I shall come back to that in a moment.

I think that it is unnecessary to elaborate the point that he did not have syphilitic aortitis. Most people who develop heart failure on the basis of syphilitic aortitis have free aortic regurgitation. A few people who have syphilitic involvement of the coronary orifices develop heart failure on the basis of the coronary closure, and a very few people, usually young men, develop heart failure on the basis of syphilitic myocarditis. I see no reason to inject any of these possibilities.

I do not believe that he had a congenital form of heart disease. I do not see any evidence in the auscultation or by x-ray that would permit me to judge that. No statement is made about cyanosis except that he became cyanotic in the last days of his life, so I think we can assume that he was not cyanotic before that day.

Now we come to the electrocardiogram. An alternative or possibly an addition to the diagnosis of aortic stenosis is the diagnosis of diffuse myocardial disease due to repeated coronary occlusions. I say "repeated" because there is no mention in the history of any attacks of sufficient magnitude to have given him symptoms, and because he had the small complexes and the relatively flat T waves that one often sees with rather diffuse myocardial disease. Aortic stenosis is usually accompanied by a normal sinus rhythm if it is the only valvular lesion present. When one sees a patient with aortic stenosis who has auricular fibrillation, he looks eagerly for evidence of mitral stenosis in addition. This does not appeal to me as an ideally mitral-shaped heart. There is not the slightest suggestion of even a questionable mitral murmur. There is one other point in favor of coronary disease and that is that he certainly had a high degree of auriculoventricular block. He had a complete block at the time the electrocardiogram was taken, and usually the heart rate is below 50. Coronary disease

is certainly the commonest cause of auriculoventricular block. Digitalis presumably accounted for a certain degree of the block.

I am inclined to conclude, on the basis of somewhat uncertain signs, that this patient had as his primary variety of heart disease an aortic stenosis. I think there is no reason to doubt that he also had a diffuse myocarditis, even though the Q wave was upright.

The third question I should like to commit myself on is the nature of the terminal anuria. I can think of three or four vascular mechanisms that give an anuria. An aortic dissecting aneurysm with compression of the renal arteries has been known to produce anuria, but there is no reason to suspect that this man had a dissecting aneurysm. The second one has certain attractions, although the thought is rather far afield, that is, a thrombosis of the vena cava with occlusion of the renal veins. There have been a number of cases reported. It is rare but not impossible. It is almost always accompanied either by a great deal more evidence of venous thrombosis in the legs or by obvious collateral circulation around the groins, or both. The third is an embolic occlusion of the renal arteries or a sufficiently sizable number of infarcts in both kidneys so that anuria results. It is much likelier to come about from the type of embolus that originates in the fibrillating auricle than it is from acute or subacute endocarditis. On the whole I should be inclined to think, although I find no evidence of any other embolic incidents anywhere in the body, that this anuria was due to an acute interference with renal circulation on the basis of embolism. It may be that for a brief period this patient's fibrillation ceased, to be replaced by a normal rhythm, which is one of the ideal situations for multiple embolism and may have been the thing that explains this picture. Whenever one sees a man of fifty-nine who has progressive edema without previous evidence of cardiac failure, one is reminded that there is a type of tuberculosis of the pericardium that is particularly common in old men.

Because he was a fifty-nine-year-old man who had a large heart, a very rapidly progressive affair, with no fever, no x-ray evidence and no physical signs, I shall rest the case on four diagnoses: heart failure, aortic stenosis, diffuse myocardial disease associated with coronary arterial disease, and infarction of the kidney.

DR. CHESTER M. JONES: Is it not curious that the edema was from the abdomen down, so to speak, and that he had no engorged neck veins and other signs of right-sided failure, and no left-sided failure, as evidenced by orthopnea and dyspnea, until the terminal event?

DR. BURWELL: Those are all "curious incidents" as Sherlock Holmes would have said. Some can be rationalized. As a matter of fact, exertional dyspnea was almost as early a symptom as slight swelling of the ankles. Exertional dyspnea presumably meant that he had a slight amount of pulmonary congestion. It is possible, although I do not know and I cannot tell from the x-ray film, that he was somewhat emphysematous. There is no statement to that effect. He ended up by having orthopnea. That is one of the reasons I am inclined to think that coronary heart disease was important. I believe that the right heart must have broken down with a relatively small amount of elevation of pulmonary pressure.

A PHYSICIAN: Was there a fall in blood pressure?

DR. CASTLEMAN: It was never very high, being 155 systolic when he came in. Just before he died it was 145 systolic, 65 diastolic. It stayed about the same throughout.

CLINICAL DIAGNOSES

Arteriosclerotic heart disease, with congestive failure.
Renal failure and uremia (?cause).

DR. BURWELL'S DIAGNOSES

Congestive heart failure.
Aortic stenosis.
Myocardial disease, based on coronary-artery disease.
Infarction of kidney.

ANATOMICAL DIAGNOSES

Endocarditis, chronic, rheumatic, with moderate aortic and mitral stenosis and slight tricuspid stenosis.
Coronary sclerosis.
Myocardial fibrosis.
Acute glomerulonephritis.
Endocarditis, acute, terminal: mitral and aortic.
Pericarditis, acute and chronic.
Congestive cardiac failure.
Congestion of liver.
Ascites.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: On the four counts that Dr. Burwell mentioned, he was correct on three. This man had heart failure. At the time of autopsy, ascites and severe chronic passive congestion of the liver were found. The heart was quite large, weighing 600 gm. He had aortic stenosis of the calcareous type, but it was mild as compared with some that we have seen. He also had a moderate degree of mitral stenosis, with thickening of the chordae tendineae, and in addition, slight involvement of the tricuspid valve; so that there is no question that he had rheumatic heart disease. There were superimposed on the mitral and aortic valves tiny

vegetations, which were merely evidence of an acute terminal endocarditis. The coronary arteries were markedly sclerotic, being narrowed in some places to pinpoint lumens. Throughout the myocardium there were small areas of fibrosis, but nothing at all recent.

The kidneys were very striking. They weighed over 600 gm., about twice the normal size, and were markedly swollen, with numerous red depressed areas scattered throughout. Microscopic examination showed old vascular disease, which accounted for the depressed areas. Every glomerular tuft was markedly swollen and filled with polymorphonuclears — findings characteristic of an acute glomerulonephritis and undoubtedly the cause of the anuria. Most of the glomeruli contained 40 to 50 polymorphonuclear cells. The tubules were swollen but contained no red cells.

DR. BURWELL: I ought to say why I ruled out tricuspid stenosis. The major reason was that he was so well up to the time he developed failure. Most people with serious tricuspid stenosis have had venous congestion of the liver for a long time. Since this patient did not have a chronically enlarged liver, I laid that diagnosis aside.

DR. CASTLEMAN: The stenosis of the mitral valve was not marked, and the tricuspid disease, although definite, was only slight. He had a pericarditis that was both old and recent.

CASE 30362

PRESENTATION OF CASE

First admission. A sixty-year-old housewife entered the hospital because of intestinal obstruction.

Twenty-two years before entry the patient had an appendectomy, and ten years later an operation for fibroids of the uterus. Since that time she had had repeated attacks of abdominal pain, tenderness and distention, relieved by medication prescribed by her family physician. For the two years preceding entry, whenever the stools were formed, they were ribbon-like; otherwise they consisted of watery fluid. On two occasions she had passed bright-red blood. Seven weeks before entry she had a severe attack of abdominal pain and was completely obstructed and distended for three days; she was relieved for three days but again became obstructed and distended for three days. At that time she first noticed a tender stationary lump in the left side of the abdomen. She had lost about 15 pounds.

Physical examination showed a well-developed pale woman with evidence of recent weight loss. The abdomen was protuberant. In the left midabdomen was a hard mass the size of a golf ball, which was extremely tender and slightly movable. No other organs or masses were palpable.

The blood pressure was 140 systolic, 70 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,210,000, with 65 per cent hemoglobin. A white-cell count was 12,500, with 76 per cent neutrophils. The urine was normal. The stools were guaiac negative. Plain x-ray films of the abdomen showed the proximal half of the colon to be dilated and filled with feces and a small quantity of gas extending slightly to the left of the midtransverse colon.

On the third hospital day an exploratory laparotomy revealed a colloid adenocarcinoma of the splenic flexure. A Mikulicz resection was performed. The distal loop of the bowel was sutured to the lateral abdominal wall to prevent the small bowel from getting into the denuded area.

The patient did well for about twelve days, but subsequently began to have attacks of lower abdominal cramps associated with profuse bowel movements. The abdomen became distended during these attacks. In the course of the next month and a half, however, these disappeared; a clamp was then applied to the stoma, and a good spur cut through. She was discharged on the sixtieth postoperative day to return in two months for closure of the colostomy.

Second admission (three months later). After discharge the patient felt well and gained 12 to 15 pounds. The colostomy had worked well until recently, when she noticed a little bright-red blood mixed with the stools and a little bleeding from the colostomy opening.

Physical examination was essentially negative.

On the fifth hospital day the colostomy was closed. Postoperatively she was bothered by impacted feces in the rectum and, when relieved of this, developed diarrhea with abdominal cramps of the type that she had had for years. Subsequently, however, the bowel movements became normal and she was discharged on the eleventh postoperative day.

Third admission (twenty-seven months later). Following discharge the patient did well for some time but presumably had further symptoms of obstruction and was operated on in a community hospital for lysis of adhesions. She was then apparently well until ten or twelve days before re-entry, when she developed severe abdominal cramps and became distended. She was taken to the same outside hospital, where an ileostomy was performed. She developed a fecal fistula in the wound, the cramps persisted, and she was transferred to this hospital.

Physical examination showed tenderness in the abdomen, which was not greatly distended. A small rubber tube protruded from the left side at the level of the umbilicus. There was a fecal fistula to the right of and inferior to the umbilicus, with considerable porky induration about the fistula

and over the central part of the abdomen, associated with cramps. When the abdomen tightened, it bulged, peristalsis increased, and then gas and feces extruded.

Examination of the blood showed a white-cell count of 10,400, with 75 per cent neutrophils. The serum chloride was 87 milliequiv. per liter, and the protein 5.1 gm. per 100 cc.

The patient was given a transfusion, and an enterostomy was performed. Postoperatively there was some relief, but she continued to have attacks of abdominal cramps. On the sixteenth day she had a spontaneous bowel movement by rectum. She gradually improved. The enterostomy tube was clamped and taken out. Drainage stopped, and she was discharged on the forty-third hospital day.

Fourth admission (six years later). Following discharge the patient did well until one year before re-entry, when she noted that the stools were covered with blood. Ten days before admission she became obstructed, with marked distention. Four days later she had a bout of severe abdominal pain, followed two days later by the passage of small amounts of blood with the stools on three or four occasions. Two days before entry she had a massive hemorrhage and apparently went into shock, since she awoke lying on the bathroom floor without any recollection of falling, but with bruises on the face and head. She was brought into the hospital shortly thereafter. No additional information was available.

Physical examination showed a pale, thin woman in no distress. There was considerable evidence of weight loss. The heart and lungs were normal. A small sausage-shaped nontender mass was palpable immediately above the umbilicus.

The blood pressure was 140 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood showed a hemoglobin of 9.1 gm., and a white-cell count of 7400, with 82 per cent neutrophils. The urine showed a + test for albumin. The stools were tarry and liquid, with a + + + guaiac test. The nonprotein nitrogen was 25 mg. per 100 cc., and the serum protein 5.8 gm. Barium examination of the colon showed an area of narrowing toward the lower end of the descending colon, which fluoroscopically was thought to be due to spasm but on the films was suggestive of an annular filling defect. No obstruction to the free flow of barium was encountered. In the midtransverse colon was an annular defect measuring 8 cm. in length, with an irregular lumen and shelf formation at either end. This defect was constant and coincided with the sausage-shaped mass in the abdomen. The right colon filled normally. A postevacuation film showed complete contraction of the colon and that most of the barium had been expelled; the filling defect in the transverse colon showed no change in its configuration, and the appearance of the narrowing at the lower end of the descending colon was less conclusive.

The patient was given several transfusions, and on the seventeenth hospital day an operation was performed.

Differential Diagnosis

Dr. Ira T. Nathanson: The findings in this patient at the time of the last admission are those of a lesion of the colon. Questions arise whether the lesion was benign or malignant and whether it was related to the previous illness.

One may first consider the possibilities of a benign lesion. Chronic granulomas, such as tuberculosis and syphilis, may occur in the colon. Tuberculosis may exist in the colon as a localized process either in the hyperplastic or ulcerative form. In a fairly high percentage of cases, however, it is an accompaniment of the disease elsewhere and is usually confined to the cecum and ascending colon. The localized type of disease may produce obstruction and involve the bowel in an annular fashion when deep ulceration occurs. A mass may sometimes be palpated, but massive bleeding is rare, although it may occur in the ulcerative type. The apparent absence of extracolonic tuberculosis, the location of the lesion, the massive bleeding and the past history seem to rule out tuberculosis. Syphilis is certainly a rare entity especially without other evidence and, like sarcoid, which is said to occur in the large bowel, can be dismissed.

Chronic diverticulitis is a remote possibility. In general, the process is diffuse, and in well over half the cases it involves the sigmoid. When other parts of the colon are affected it is unusual not to have coincident lesions in the sigmoid. The symptoms prior to and soon after the resection of the splenic flexure may have been caused by diverticulitis, since carcinoma and diverticulitis may co-exist. I should, however, expect better x-ray evidence, as well as other signs and symptoms between the third and fourth admissions. Finally, bleeding is a relatively rare symptom in diverticulitis.

Segmental ulcerative colitis may also be mentioned. As a rule it appears in young people, the symptoms are profound, and it almost always involves the rectum and sigmoid colon. X-ray examination usually reveals characteristic signs, particularly evidence of inflammation of the mucosa, in addition to a defect. Furthermore, proctoscopic examination usually yields significant information.

Of the benign tumors, which include many varieties, adenomas or polyps deserve the only consideration. These are frequently multiple and occur with greatest frequency in the left half of the colon, particularly the lower portion. Occasionally, they are of sufficient size to produce obstructive symptoms and may ulcerate and bleed. They seldom

become large enough to be palpated on abdominal examination and are rarely, if ever, capable of producing the picture of an annular defect by x-ray examination. Intussusception, which is usually due to a polyp that has ulcerated and bled, may mimic the present picture; however, shelf formation, as seen by x-ray examination, is apparent at only one end.

Finally, we arrive at the most likely diagnosis. The symptoms, physical signs, laboratory evidence and x-ray findings are compatible with a malignant neoplasm of the colon. The decision must be made whether this was a carcinoma or one of the rarer lesions, such as a malignant lymphoma, a malignant carcinoid or even a malignant melanoma. Malignant lymphoma arises most frequently in the region of the cecum and from the submucosal lymphoid tissue of the bowel wall. It follows the cleavage planes and therefore may grow to a considerable size before obstruction, annular constriction and ulceration with hemorrhage appear. The other lesions are only of academic interest.

It therefore seems apparent that the syndrome was produced by carcinoma. Two questions arise that must be answered. Was this a new or recurrent tumor? Was it a single or a double lesion? The disease may have represented an extension of the previous carcinoma of the splenic flexure. Processes were described in the midtransverse colon and in the lower end of the descending colon. Each of these is a considerable distance from the first carcinoma, and from the x-ray report one may assume an area of normal bowel in the region of the bowel resection, which was between the two lesions described. Moreover, it is very unusual to find a recurrence of a cancer of the colon after a five-year interval of freedom from disease. According to the history, the final symptoms appeared about seven and a half years after the first admission. Hence, there seems to be little doubt that the original lesion was cured. It is well recognized that multiple primary cancers of the colon may occur simultaneously or successively over a period of years. When two or more cancers occur simultaneously they frequently arise in pre-existing polyps. Successive malignant changes in polyps, however, are also possible. In this case such a situation may have occurred. Thus it is problematical whether this was a single or a double lesion and whether the origin was in a polyp. The absence of polyps by x-ray examination, even though they are occasionally difficult to demonstrate, and the variability of the findings in the descending colon suggest a single primary cancer of the transverse colon. Such a lesion can arise in a polyp, and if one accepts the presence of a second cancer in the descending colon, then origin from a polyp is likely. The x-ray defect in the lower colon seems to have been due to spasm, which often occurs, especially after a bowel resection.

If one ventures a guess concerning the type of such a neoplasm, it should be based on the location of the lesion, the form most frequently seen at that site, and the history. Cancer of the transverse colon is usually of the scirrhous type, which produces annular constriction of the colon. It may remain localized for a relatively long period of time and thus may attain considerable size before producing severe symptoms. The type of lesion seen oftenest is an adenocarcinoma, particularly if it arises on the basis of a polyp. In general they are of low to moderate malignancy.

Clinical Diagnosis

Carcinoma of transverse colon.

Dr. Nathanson's Diagnosis

Primary adenocarcinoma of transverse colon (moderate malignancy).

Anatomical Diagnosis

Primary adenocarcinoma (Grade II) of transverse colon.

Pathological Discussion

Dr. Benjamin Castleman: As Dr. Nathanson has indicated, once having decided that the lesion in the transverse colon was a carcinoma, it is interesting to speculate whether the lesion was a recurrence or a new tumor. The resected specimen of transverse colon, which was 34 cm. long, contained a large annular ulcerated carcinoma 8 cm. in length. The site of the previous well-healed enteroenterostomy was 17 cm. away from the tumor, so that I believe there can be no question that the carcinoma was a new one rather than a recurrence. It was of a moderate degree of malignancy.

Because of the numerous previous abdominal operations, the peritoneal cavity was completely obliterated by adhesions, except for a small area in the right upper quadrant, and the surgeon had a difficult time isolating the proximal transverse colon for resection in order to make sure of the blood supply of the distal portion. Finally, an end-to-side anastomosis between the ascending colon and the sigmoid was performed. No lesion was observed in the descending colon.

The patient left the hospital on the twenty-third postoperative day. Since the regional lymph nodes were not involved, the prognosis should be good.

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MASSACHUSETTS EMIC PROGRAM

Worry is a dangerous liability to men in combat, and release from the financial exigencies of impending parenthood is one benefit of the Emergency Maternity and Infant Care Program the importance of which cannot be minimized from either the medical or the military viewpoint. More than 1900 Massachusetts physicians have signified their willingness to provide medical care for the 12,184 cases already authorized by the program, which means, as stated elsewhere in this issue of the *Journal*, that more than 10,000 servicemen serving at home and abroad are fighting the war with the assurance of complete, competent medical care for their wives — not only during pregnancy but also for any acute condition beginning in the first six weeks post partum — and for their infants, including care during sickness and immunization against smallpox, diphtheria and whooping cough. Similarly, the vast majority of Massachusetts hospitals are participating in this wartime service. That all this is greatly appreciated is evidenced by the many letters from servicemen received by the Massachusetts Department of Public Health, which, incidentally, deserves unstinted praise for the way in which the program has been organized and administered in the Commonwealth.

The EMIC program was created to relieve servicemen of the four lowest pay grades of the burden of debt through furnishing this specific type of medical care for their wives and infants, and is not intended to benefit any other group. The rules and regulations were promulgated by the Children's Bureau of the United States Department of Labor, and the states merely act as administrative agencies. The latter are not permitted a great deal of latitude in interpretation except to modify, subject to the approval of the Children's Bureau, regulations that conflict with state laws and practices. All fee schedules used in this program are within the permissive limits set by the Children's Bureau and are subject to the latter's approval.

The original program was planned for the general practitioner, but liberalization of its activities now calls for the services of specialists as qualified consultants. Of course, if a specialist is willing, he may care for a patient as an attending physician.

The EMIC program as a whole and certain of its rules and regulations have been severely criticized and even rejected by several national and state medical societies largely because it is believed that the program is an entering wedge for "state medicine." It should be borne in mind, however, that, in addition to contributing to the morale of the armed forces, the program is an emergency procedure, that, according to the Children's Bureau, it will terminate six months after the war is ended and that, in many sections of the country, it has provided maternal and infant care that would otherwise have been either inadequate or unavailable. The enthusiastic response of the physicians

of Massachusetts attests to their willingness further to assist in the war effort, even though many of them do not approve of certain of the principles involved in this type of medical care. Furthermore, the outcome of the program may provide a means of determining whether this is the type of medical care that the people of the United States want as a steady diet.

"COLD VACCINES"

EACH year as the summer comes to a close and the season for colds begins, persons who regularly suffer from frequent colds and their sequelae seek relief from a recurrence of their difficulties. This is especially true among persons who have had a particularly bad time with colds during the preceding year. Because of the large number of persons afflicted each year, almost every physician is confronted with such cases and has to cope with this problem. Moreover, many physicians are victims of frequent colds, which they are desirous of preventing.

The great majority of physicians frankly admit that they do not know of any method of preventing or reducing the incidence of colds, except perhaps by general hygienic measures, which are thought to "increase resistance" and perhaps also by limiting exposure through contact with persons already manifesting the symptoms of a cold. Neither of these methods can be expected to yield startling beneficial results. Many physicians, on the other hand, state that, although they have no specific means of preventing the colds, the etiologic agent of which is presumably a virus, they are hopeful of preventing the sequelae of colds, which are usually caused by the common bacterial pathogens of the respiratory tract. They therefore resort to vaccines prepared against the more frequent bacteria, namely, pneumococci, streptococci, staphylococci, influenza bacilli and, perhaps, Friedländer bacilli. They hope thus to immunize the sufferers in some specific or perhaps nonspecific way against secondary infections with these organisms.

It is now well known that most of these respiratory pathogens are represented by numerous specific types and that immunity is for the most part type-specific in character. In other words, it seems futile to attempt immunization against all or even any one group of these organisms. Yet these bacterial vaccines, which are obligingly prepared even by reputable pharmaceutical firms in response to the demand, are regularly given by many physicians in a "shotgun" manner. Carefully controlled clinical experiments on the prevention of colds are difficult to carry out. When they have been done, it is only rarely that any beneficial results from these vaccines have been noted.

In wartime, since colds constitute the major cause of absenteeism from work, their prevention becomes an acute problem. One of the recent attempts to conduct a controlled experiment with commercial cold vaccines has been reported by McGee and his associates* in the Medical Department of the Hercules Powder Company. These industrial physicians used three oral and two parenteral vaccines that are currently offered by commercial laboratories for prophylaxis against the common cold. Their study was carried out in a group of over 1000 industrial and office workers during the October-to-April seasons of 1941 and 1942 and of 1942 and 1943. Placebos were given to some of the subjects, who thus served as controls. Their results are worth quoting:

> An examination of the average number of colds suffered per person, the number of days lost per person because of these infections and the number of days lost per infection suggests no outstanding value for any vaccine included in this clinical test. By assigning possible significance to slight differences to the arithmetical averages of the various categories shown in the table, one notes the following: the fewest colds developed in groups receiving either Vacagen, Sharp and Dohme vaccine for parenteral use or a placebo by mouth; groups receiving Oravax, a placebo (orally or hypodermically) or taking no prophylactic medication at all lost fewest days from work because of colds; groups receiving a placebo hypodermically, Oravax or nothing at all have the mildest infections (measured by the length of absence per acute cold reported).
>
> In view of the behavior of the control groups, we find no evidence of clearly effective prophylaxis against either the frequency or the severity (including complications) of the common cold from the use of any of the vaccines studied.

From these studies, McGee and his co-workers conclude, "No clearly evident protection against

*McGee, L. C., Andes, J. E., Plume, C. A., and Hinton, S. H. "Cold vaccines" and incidence of common cold. *J. A. M. A.* **124**:555-557, 1944.

the cold and related acute respiratory infections can be demonstrated in the results of this clinical trial at mass immunization." They are therefore led to the further conclusion, "The indiscriminate use of cold vaccines which are now available is not the answer to the problem of industrial absenteeism due to acute respiratory infections." Once again, it has been shown that the administration of "cold vaccines" merely means a waste of the physician's time and of the patient's money.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON PUBLICATIONS

The *Journal* lacks extra copies of the January 13, May 11 and June 1, 1944, issues. Many requests have been made by libraries and other subscribers who wish to bind Volume 230 but who did not receive those particular issues, owing to the difficulties accompanying a change of printers. If any subscribers who do not bind their copies have the January 13, May 11 and June 1 issues on hand, the *Journal* will gladly pay 15 cents for each copy left at or mailed to its office (8 Fenway, Boston 15).

RICHARD M. SMITH, *Chairman*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

EMERGENCY MATERNITY AND INFANT CARE PROGRAM

More than 10,000 prospective mothers have been accepted for care under the Emergency Maternity and Infant Care Program since it went into effect in Massachusetts last September. The total expenditure for the care of these cases will exceed $1,500,000, which will be allotted to physicians and hospitals. That this program has proved a boon to the thousands of wives and babies of Massachusetts servicemen in the fourth, fifth, sixth and seventh pay grades is quickly recognized.

Effective August 1, additional physician's services were made available to the wives and infants *accepted for care* under this program. Each physician will be sent a statement through the mail about the program, and a complete description is available either in the library or in the superintendent's office of each participating hospital. The changes are as follows:

Maternity Care

Medical. The attending physician may receive payment for the treatment of conditions not attributable to pregnancy, both in the home or in the hospital during pregnancy and the post-partum period. Office treatment of intercurrent nonobstetric conditions is included in the overall fee for maternity care.

Surgical. The attending physician may receive payment for surgical conditions not attributable to pregnancy (such as appendicitis) during the maternity period, which includes a six-week post-partum period, *provided* that he qualifies as a consultant in a surgical specialty. If the attending physician does not qualify as a consultant in a surgical specialty, he may call a consultant, who will receive payment for any operation he may perform. (There has been no change in the ruling that the attending physician — even though qualified as a consultant — must call another consultant for an *obstetric operation* if an additional charge for the operation is to be made. No extra fee may be granted to the attending physician for an obstetric operation.)

Continuing care. If a serious *acute* condition beginning before the end of the six-week post-partum period continues uninterruptedly beyond that period (as in phlebitis), the attending physician may be paid for home or hospital care of this condition continuing beyond the six-week post-partum period. Hospitalization at ward cost, bedside nursing and consultant service may also be paid for under these funds.

Note: All services for which payment is expected must be requested at the *beginning of the illness*. This request may be made by the physician or hospital by letter or by telephone (CAPitol 4600).

These new services are not retroactive, and payment will not be made for conditions occurring prior to August 1, 1944. Bills for professional services should be sent only after authorization has been received.

Infant Care

Immunizations. Immunizations for smallpox, diphtheria and whooping cough are now included in the program. A maximum payment of $6.00 for this service will be made to the private physician if no other immunization facilities are locally available. Where immunization facilities are available at local health-department clinics, no payment may be made. If given at pediatric clinics or well-child conferences, the usual clinic fee may be paid, not to exceed the maximum per visit of 50 cents.

Biologicals. Whooping cough, smallpox, diphtheria and combined whooping cough and diphtheria biologicals are furnished free for infants authorized under this program. An addressed postcard requesting biologicals will be attached to the authorization, and this should be mailed directly to the Antitoxin and Vaccine Laboratory by the attending physician.

Crippling conditions. Infants with crippling conditions will be transferred to Services for Crippled Children.

Circumcision. A fee for circumcision is not included under this program.

Consultant Service

Services of a consultant are available provided he meets the standards described in the July 6 issue of the *Journal*, and such services are authorized.

Assistant Service

If no member of the resident hospital staff is available, a private physician may be paid for assisting at a major operation.

BOOK REVIEW

Walter Reed: Doctor in uniform. By L. N. Wood. 8°, cloth, 277 pp., with 18 illustrations. New York: Julian Messner, Incorporated, 1943. $2.50.

The life of Walter Reed, one of the pioneers in bacteriology in this country, whose fame rests largely on his experiments in Havana, carried out on human beings, which show that the common house mosquito was responsible for the spread of yellow fever, is well known to all members of the medical profession. Mrs. Wood has taken this fascinating story and written it in a simple, straightforward manner, particularly aimed at a popularization of Reed's life for children.

The book is exceptionally well written and should have a wide appeal, for the author is particularly skillful in drawing a picture of an outstanding man in American medicine. The account is accurate, and there is an excellent bibliography, as well as an adequate index. The illustrations are particularly good, and the whole book gives a splendid picture of the man and his accomplishments. It may be highly recommended.

(*Notices on page xvii*)